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Editorial

In the process of evolution, it was the development of a circulatory system that enabled different tissues to develop more specialized functions. In mammals and man, the vascular system, itself a highly specialized organ system, by maintaining tissue perfusion integrates the different metabolic process of the various organs and tissues and thus maintains the body's internal milieu. Its proper function is necessary for the health of all body organs and its disease has become a major cause of morbidity and death in this present age.

The article on vascular resistance reviews the normal physiological mechanisms that alter and control resistance to blood flow. As medical students we are taught the controls of blood pressure, but perhaps a more important parameter is that of blood flow; how much and to where. A hypertensive person in shock may exhibit "normal" blood flow while in surgery especially cardiovascular, blood pressure may be below "normal" and yet blood flow is adequate. Although various different flow-meters are available, measuring blood flow has always been difficult because it usually involved inserting the flow-meter in a vessel. The dye dilution technique is now widely used to measure cardiac output. Further new techniques with radioactive isotopes and radio-opaque dyes are presently being used experimentally to study blood flow to different organs. Perhaps, in the future, we shall talk about blood flow with the same familiarity as we do blood pressure today.

The article on sludging of blood brings out some of the extremely interesting and controversial developments that have opened up with the advent of microscopic study of living tissue. When one realizes that the smallest blood vessels are slightly smaller in diameter than the blood cells, one can understand the importance that the interaction between blood cells themselves and with the vessel wall plays in blood flow. There are probably many experimental errors and artefacts in the results because of the delicate technique used in this study, but it is refreshing to see that physicians are now able to see what is actually going on instead of just theorizing with experimental models.

Virchow's triad: blood flow, blood elements, and the vessel wall, has dominated the concept of thrombus formation for many years. The article on thrombophlebitis and phlebothrombosis emphasizes Virchow's role in elucidating the pathogenesis of these disorders, which resulted in a more intelligent approach to the diagnosis and treatment. With modern surgical technique and the heart-lung machine, treatment of massive pulmonary embolism is now a possibility. But, because many of the signs and symptoms are non-specific, the diagnosis is often difficult. Three new diagnostic tools have proven useful: arterial-alveolar pCO_2 gradient, pulmonary scan and pulmonary angiography. Because some alveolar air is leaving alveoli which are not perfused with blood and thus without the added CO_2, and because excess blood is passing by normally aerated alveoli, there will be a greater difference in the pCO_2 of arterial blood and that of the expired alveolar air. The pulmonary scan technique using radioactive isotopes will demonstrate areas of the lung not perfused with blood. However, this technique is usually too slow to be used when emergency pulmonary embolectomy is to be performed. In spite of the risks of pulmonary angiography, this will usually demonstrate the size and position of the embolus, and will probably be widely used when the surgical technique has been perfected.

EDITORIAL

With the advent of electron microscopy, more complex histochemical techniques, and more biochemical assay systems, the research into atherosclerosis has progressed from the gross pathological descriptions of Rokitansky to the elucidating of basic metabolic pathways. Lipid metabolism, long the field of the pure biochemist and endocrinologist, now dominates the current research of the clinical pathologist interested in atherosclerosis. As is pointed out in this issue atherosclerosis is not considered as just a inevitable, relentless complication of ageing, but rather as a dynamic inevitable disorder with many variables many as yet undiscovered or ill-understood.

Studies on the coagulation mechanism have also broached the boundaries of biochemistry as evidenced by the great interest in the function of ADP and its role with the platelet in initiating coagulation. An interesting offshoot of these investigations, still very controversial and highly experimental is the relation of ADP, platelets, and blood viscosity to myocardial infarction and the question of post-infarct anticoagulant therapy. Though several large scale studies have shown no increased survival rate in patients treated with anticoagulants after infarction, the theoretical advantage and certain interesting experimental studies, one of which is mentioned in the student research article, suggest that there may indeed be some benefit to this procedure.

The recent exciting developments in the field of immunology, and the identification of many different circulating auto-antibodies in the collagen disorders is prompting investigators to place more importance in the recognition of vasculitis, a predominant feature of immune diseases. The question of inter-relationships among vasculitides, their underlying etiology and their treatment is still much in the forefront in consideration of the diseases. With the current experimental evidence of virus-type infection producing Polyarteritis, Lupus Erythematosus and Rheumatoid Arthritis in animials, and some tentative evidence of a infectious etiology for Rheumatoid Arthritis in man, the possibility of the vasculitides themselves being all hypersensitivity diseases initiated by some as yet undiscovered virus or virus-like organism is being actively investigated. The article on the vasculitides is thus included to help orientate the reader as to most of the specific disorders considered as vasculitides, in the hope that with devleopments to come in the near future, some pattern in this hodge-podge may be discernible and more easily understood.

The editors would like to thank our guest editor Dr. Gardner McMillan for his interesting comments on the importance of vascular disease. We are indeed fortunate to have his ideas, as well as his presence at our university.

We trust that this issue will help impress upon the reader the new, interesting, challenging, and dynamic aspects in the vascular diseases—a field which in the future will be seen to have an even more varied and important status.

R.I.H. M.B.

Guest Editorial

DR. GARDINER MacMILLAN,
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Former Professor and Head of the Department of Pathology at McGill University, is now Professor in the Department of Pathology at the University of Toronto. He has published over forty articles on the etiology of, and experimental research into atherosclerosis, and is considered by many researchers as one of the foremost experts on vascular disease.

Vascular Disease

This group of diseases—the catalogues of disease have many, many entries listed under the heart and blood vessels—becomes more and more important in our world as a cause of disability or death. Today, with powerful means to prevent and cure bacterial diseases, with high quality medical and surgical care, and with affluence and an abundance of food, the vascular diseases that become manifest in mature and old age are increasing in prevalence. Coronary heart disease, cerebrovascular accidents and hypertensive disease are so common that they are together the greatest killers in the industrialized world.

As historical time goes, medical interest in most of these diseases is very recent. Indeed, it is within the professional experience of many physicians who are still alive and active. Myocardial infarction was first described as a clinical entity in 1910 by Obrastzow and Straschezko, and a little later by Herrick. It did not have wide clinical acceptance until the mid-1920's when the electrocardiograph came into use. Arteriosclerosis was under investigation from about the same time and important early work was done in Toronto by Oskar Klotz. However, it was not until the 1930's and particularly the 1940's that the field became an active one for research. The clinical measurement of the blood pressure began by the turn of the century. Interest in the etiology and pathogenesis of hypertension dates from the 1920's.

By contrast, there is now much basic and applied research in cardiovascular disease of all kinds. There were 662 abstracts printed just for the last annual scientific meeting of the American Heart Association. Because cardiovascular disease is a grouping of many different disease entities and processes, no single breakthrough of knowledge can be expected to solve them all. However, the systematic accumulation of knowledge is establishing in detail their fundamental normal and abnormal processes and is bringing a very high degree of sophistication and skill to the clinical diagnosis and care of the cardiovascular patient.

Peripheral Vascular Resistance

R. I. Hilliard 6T7

The complex assortment of various sized tubes that make up the peripheral vascular tree provides the important function of supplying vital nutrients to and removing excess materials from the various tissues and organs. It is this blood perfusion through the different organs and tissues that is of chief concern to the anesthetist or the intern in the emergency department or the nurse who diligently checks her patient's blood pressure and pulse. Certainly tissue perfusion will depend on the heart and its capacity to pump blood into the arterial system, but it will also depend on the reactions of the vessel system. Blood flow through the body or through a vascular bed can be considered as the blood pressure gradient divided by the vessel resistance. It is this peripheral vascular resistance and its normal physiological control that is the subject of this paper.

A. General Resistance Factors

The vascular system can be considered as a parallel-coupled set of resistances: the aorta and large arteries with elastic tissue which damp the oscillating pressure produced by the heart; the resistance vessels; the sphincter vessels; the capillaries or exchange vessels; the capacitance vessels (the venous compartment) and the shunt vessels (these occur mainly in the skin).

In terms of blood volume, the normal distribution is: aorta—2%, arteries—8%, arterioles—1%, capillaries —5%, veins—50⁺%, heart—12%, pulmonary system —18%.

Resistance to blood flow across any vessel will depend on the vessel length, vessel radius, and blood viscosity:

$$R = k \frac{\text{vessel length} \times \text{blood viscosity}}{\text{fourth power of vessel radius}}$$

1. The resistance to blood flow will vary directly with the length of the vessel. Normally, with the one exception of the pulmonary system, vessel length remains fairly constant, so that this is not an important factor in the change of vessel resistance.

2. Vessel resistance varies inversely with the fourth power of the radius of the vessel. The vessel radius may be changed actively by a change in the degree of the vascular smooth muscle tone, controlled by local factors, and neurogenic and hormonal stimuli, or passively due to changes in the transmural pressure, i.e. the difference between intraluminal and extramural pressure. The vessel may dilate passively subsequent to a rise in cardiac output, increased downstream resistance or with a dependent position in relation to the heart. Thus, for example, flow through a limb may increase after elevation of cardiac output in part because of the decreased resistance in distended vessels. A fall in transmural pressure may result from a fall in cardiac output, decreased downstream resistance, elevation above the heart level, or an increase in the extravascular pressure which may occur particularly in a rigid or semi-rigid enclosure such as the kidney or cranial cavity.

The vessel radius may also vary passively because of organic changes in the vessel wall such as narrowing with wall edema, subintimal hemorrhage, fibrous intimal thickening, atherosclerosis, inflammation or coarctation. In the normal vessel, the question of wall edema is extremely interesting. Lowering the tonicity of the blood by the rapid infusion of a hypotonic solution of NaCl or dextrose causes constriction of arterioles. But, whether this constriction is due to wall overhydration and consequent passive encroachment upon the lumen or to active constriction remains to be determined. Dilation may result passively from wall dehydration, arteriosclerosis, pyogenic and syphilitic infection or a congenital aneurysm.

3. Blood flow resistance will increase with an increased viscosity of the blood. The major factor is the blood cell concentration, although the plasma proteins also exert an effect. Below a hematocrit of 30%, there is little change in viscosity; at higher hematocrit levels, there is a non-linear direct relationship between red cell concentration and viscosity. A hematocrit of 45% appears to be the best compromise between increased red cell concentration reducing blood flow and decreased red cell concentration decreasing the oxygen carrying capacity of the blood. Abnormal blood flows such as agglutinated cells, rouleaux formation and sickle cells will also increase viscosity.

B. Local Control of Vessel Resistance

There are certain processes which operate locally in a vascular bed to maintain certain factors constant in the face of various externally or internally induced stress.

1. Physical. Perfusion studies of the various organs indicate that there is some autoregulation of blood flow such that despite fluctuations in perfusion pressure in the range of 50-90 mm Hg (and even as high as 200 mm Hg.) the blood flow remains relatively constant. This is particularly effective in the renal, myocardial and cerebral circulation, moderately effective in muscle, the intestinal and hepatic circulation and not effective in the skin circulation. There have been various theories to explain this autoregulation:

a) It is merely a passive change, a result of a change in interstitial and venous pressure. With increased perfusion pressures, there is increased capillary filtration and thus increased tissue pressure which would tend to passively decrease the size of the vessels.

b) There may be a feedback response involving some tissue metabolite which may be O_2, CO_2, H^+, ATP or pyruvate. A decrease in pressure and tissue perfusion would lead to a fall in pO_2 and a rise in the other metabolites, which might result in relaxation of vascular smooth muscle.

c) Attempts have been made for example by partial venous occlusion to demonstrate a myogenic theory for autoregulation; that the arterial wall responds directly to a rise in intraluminal pressure by an increase in its state of contraction or tone sufficient to bring about a reduction in the lumen of the vessel and presumably a decrease in blood flow. Proponents of this theory also describe a venous-arteriolar reflex, elevation of venous pressure resulting in a local reflex arteriolar constriction.

To explain this autoregulation, there is probably more than one single factor involved and the predominant factor may vary in different organs. In the kidney, glomerular filtration may be a more significant variable which affects vessel resistance possibly via the juxta-glomerular apparatus. In the heart and skeletal muscle, it may be O_2 metabolism, in the brain possibly CO_2. Autoregulation may be absent in vascular beds which have low metabolic requirements such as the skin.

2. There are certain chemical substances which locally alter the vessel radius and thus the rate of blood flow.

a) A decrease in tissue pO_2 peripherally results in vasodilation; this may result from a decrease in ATP formed in the smooth muscle cell in the presence of insufficient O_2. This is particularly important in the myocardium and skeletal muscle.

b) An increase in pCO_2 will result in vasodilation, although this effect seems to occur mainly in cerebral vessels.

c) The H^+ concentration is an important factor in cutaneous, renal and skeletal muscle vessels. A lower pH results in vasodilation while an increased pH results in increased resistance.

d) $[Ca^{++}]$ increases of even 1-2 mg% cause measurable arteriolar constriction. Increased $[K^+]$ over the range of 4-8 mEq/L causes arteriolar dilation, but at higher levels arterial constriction. $[Mg^{++}]$ is also a powerful vasodilator and decreases the responsiveness to locally injected noradrenalin. Acetate and citrate cause local vasodilation; chloride, biphosphate, sulfate, lactate, nitrate and bicarbonate have little effect.

e) Hypertonic solutions of sodium, glucose and urea result in vasodilation, but whether this is an active response on the part of the arteriolar smooth muscle or a passive change in the hydration of the vessel wall is not known.

3. A local increase in blood flow through superficial tissues after exposure to noxious influences such as inflammation, irritation, burning heat or cold may result from vasodilation of an axon reflex. This continues after the sympathetic nerve supply has been cut and even after the sensory nerve has been cut between the dorsal root ganglion and the spinal cord, but not after the sensory nerve has degenerated. It is thought that sensory pain fibers also connect with arterioles and serve a vasodilatory function.

C. Extrinsic Control of Vessel Resistance

These local controls are usually dominated by extrinsic neurogenic and hormonal controls which will cause not only a considerable change in arterial pressure but also serve a more important function of altering the distribution of blood flow between the various vascular systems. In hemorrhagic shock, cerebral and myocardial blood flow is maintained at the expense of renal, intestinal and cutaneous blood flow. In severe exercise, part of the large increase in skeletal muscle flow is at the expense of the intestinal and renal vascular systems.

1. The most widely distributed vasomotor nerves are the sympathetic adrenergic fibers which act mainly on arterioles at a theoretical alpha receptor, by the liberation of noradrenaline and adrenaline causing constriction. These unmyelinated fibers originating at the sympathetic ganglia (the transmitter substance being acetylcholine) usually discharge at a rate of 1-2 impulses/sec, but when maximally stimulated, at 10-15/sec. These are maximally effective in the cutaneous, renal and mesenteric systems, moderately effective in muscle and the spleen and in the hepatic artery and portal vein, but are of little significance in cerebral and coronary vessels. They exert an effect on arterial and aortic smooth muscle which is of little importance, but can also cause significant venous constriction. It is estimated that infused noradrenaline can shift as much as 500 cc. of blood from the veins of dependent limbs in a short time. This vasoconstriction can be blocked by: adrenergic blockers (which also block circulating noradrenaline) such as phenoxybenzamine; sympatholytic agents such as guanethidine and reserpine; and ganglionic blockers such as tetraethylammonium. In these vascular beds, release of vasoconstrictor tone accounts for the active vasodilation.

2. Circulating adrenaline has been shown to have some vasodilatory effect mainly on skeletal muscle vessels at a theoretical beta receptor. This is maximally affected by isoproterenol but not by noradrenaline and blocked by beta adrenergic blockers such as di-chloroisoproterenol or propranolol (Inderol). Whether this is

a direct effect on smooth muscle or the result of a metabolic effect and the resulting increase in vasodilator metabolites is not clearly known.

3. Skeletal muscle vessels are also supplied by sympathetic cholinergic vasodilator nerves which are inactive at rest, and whose impulses originate not from the vasodepressor medullary center but in the hypothalamus and cerebral motor cortex. They exert their major effect at the very beginning of exercise or even in anticipation of exercise, and possibly in certain emotional reactions and post-hemorrhagic fainting. (The sustained vasodilation during exercise is probably due chiefly to the formation of vasodilator metabolites.) The only other fully established sympathetic cholinergic vasodilator nerve fibers are those from the lumbar sympathetic outflow which via the hypogastric plexus result in penile erection. This function is thought to occur by both parasympathetic and sympathetic vasodilator fibers.

4. Although parasympathetic fibers are known to travel with various vessels especially cerebral, coronary and pulmonary, whether they exert any vasodilatory effect on vessels is not known. The only definitely known parasympathetic vasodilator nerves are those of the nervi erigentes.

5. Vasodilation may result from stimulation of parasympathetic cholinergic nerves supplying the salivary and possibly some intestinal glands, and sympathetic cholinergic nerves to the sweat glands (except the hands and apical areas). This is thought to be mediated by a vasodilator substance released in these glands called bradykinin.

6. Blood vessel tone may also be effected by circulating hormones:

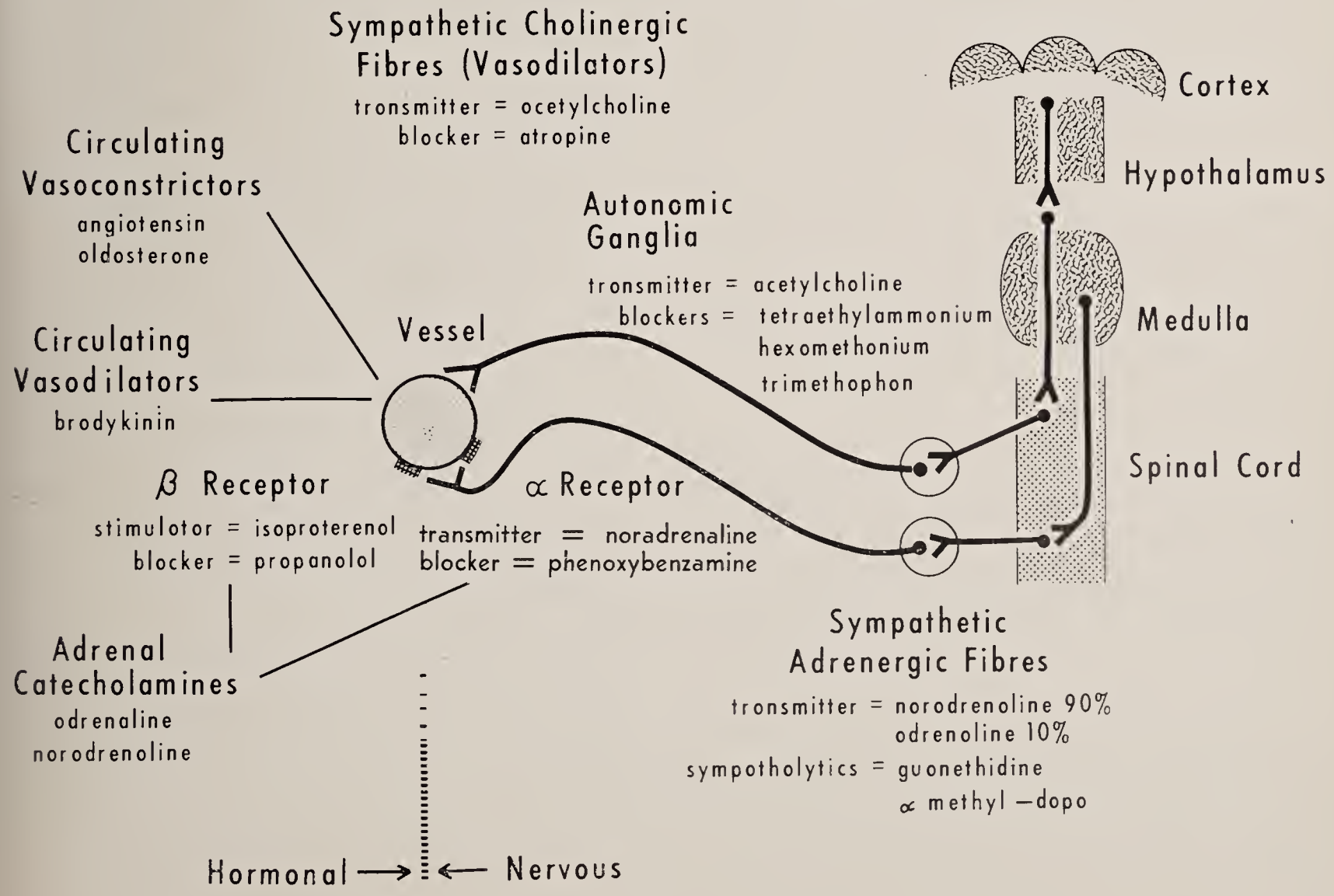
a) *Amines*

i. Adrenal catecholamines (adrenaline and noradrenaline) will affect alpha and beta receptors but are ordinarily of little importance compared with the effects of those produced by the vasoconstrictor nerves.

ii. Serotonin may cause either vasodilation or vasoconstriction depending on the degree of neurogenic tone. In the lung and kidney whose vascular tone is normally low, serotonin causes constriction; in the limb however, it dilates when neurogenic tone is high and constricts when neurogenic tone is low, and may have no effect when tone is at an intermediate level. Recent evidence has shown than the vascular changes in the carcinoid and dumping syndromes are more likely due to bradykinin than serotonin.

iii. Histamine is known to cause small vessel dilation and increase in capillary permeability.

EXTRINSIC CONTROL OF A SKELETAL MUSCLE ARTERIOLE



b) *Peptides*

i. Bradykinin as mentioned previously has a local effect and probably causes the vascular changes in the carcinoid and dumping syndromes.

ii. Angiotensin-II is a powerful arteriolar constrictor with no presently known means of blockage.

iii. Vasopressin is also a powerful arteriolar constrictor but does not usually occur in significant concentration to affect blood vessels.

c) *Steroids*

Besides its affect on renal tubular reabsorbtion of Na^+, aldosterone appears to affect the blood vessels directly causing constriction. The glucocorticoids are used in endotoxic shock but whether they have any direct effect on vessel tone is not known.

D. Areas of Central Nervous System Control

There are various centers in the central nervous system which control these neurogenic and hormonal mechanisms.

1. The preganglionic sympathetic neurons in the lateral horns of the thoracic and lumbar segments may exhibit spontaneous activity independent of afferent nerves or brain stem controls and may respond to hypoxia or hypercapnea. Further there are certain spinal vasomotor reflexes. Pain or cold stimulation of the skin may result in segmentally arranged constriction of intestinal vessels. In cases of high transection of the spinal cord, afferents from the hollow viscera may result in spinal vasomotor reflexes such as the increase in blood pressure with distension of the bladder.

2. The most essential central area for the basic control of the circulatory system is situated in the medulla oblongata. In the reticular formation in the floor of the fourth ventricle, two general areas can be outlined, one of which controls the pressor and cardioaccelerator response, the other producing an inhibitory effect. (No vasodilator fibers can be activated through the medullary depressor area.)

3. Excitatory and inhibitory neurons of the cardiovascular system can also be found in the hypothalamus. In general, the anterior portion may cause a release of constrictor tone and when stimulated by a rise in temperature responds with cutaneous vasodilation and sweating. The posterior portion may respond to lowering of temperature with vasoconstriction and increased pulse.

4. Little is known about how the cerebral cortex affects the cardio-vascular system but in association with the hypothalamus it produces vascular changes in preparation for muscular effort and in the emotional reactions.

E. Central Nervous System Reflexes

There are several basic cardiovascular reflexes mediated through these brain centers:

1. Somatic nerves. Besides the axon and spinal reflexes, sensory afferent nerves via the medulla will cause various changes in the vascular system; the rise or fall in blood pressure will depend on the strength and type of stimulus. A painful stimulus will lead to a sympathetic pressor response, while stretch stimulation of the abdominal viscera, the mesentery, peritoneum or even the anus, vagina or spermatic cord may cause a depressor response. Some reflexes occur without any general change in blood pressure, such as the facial flushing that may occur as a result of bladder distension.

2. Mechanoreceptors. The mechanoreceptors in the aortic arch and carotid sinus provide the fundamental regulation of system blood pressure, as well as compensating for gravity and hemorrhage. A fall in blood pressure results in an increase in the rate and force of heart contraction, increased vessel tone in arterioles and veins, sweating and increased adrenaline liberation from the adrenal medulla. After section of the two glossopharyngeal nerves and the vagi, a loss of 10% of the blood volume may prove fatal, while normally only hemorrhage of at least 35-45% is fatal. Afferent fibers from these mechanoreceptors also have a connection to depress the activity of the ascending reticular activating system. Other mechanoreceptors are found in the common carotids, at the root of the right subclavian artery, in the thoracic aorta, and in the mesenteric vessels. There are some pressure receptors in the pulmonary artery, stimulation of which may cause systemic hypotension and bradycardia. Similar mechanoreceptors are found in the different chambers of the heart which probably cause bradycardia, systemic hypotension and venous dilation, thus preventing overloading of the heart. The trial receptors may exert a long term influence on blood volume by reflexly affecting aldosterone and ADH production. The increase in blood pressure with elevation of intracranial pressure is not due to any pressure receptors but results from brain stem ischemia.

3. Chemoreceptors. The vasomotor center in association with the respiratory center will respond to certain chemical stimuli directly and via chemoreceptors in the carotid and aortic body. Normally these chemoreceptors have no tonic effect but are important with arterial hypoxia. Increased CO_2 and H^+ will directly stimulate these medullary centers.

4. The cerebral cortex and hypothalamus take part in certain vasomotor reflexes which may affect or bypass the medulla. During fright, emotional stress and in preparation for muscular effort, there is skeletal vasodilation with vasoconstriction in other areas, and an increase in sympathetic stimulation of the heart and adrenal medulla. During embarrassment there may be cutaneous vasodilation and increased sweating. The vas-

cular changes may be just the face and shoulders, and are probably due to release of sympathetic tone and bradykinin production. With hostility and resentment, there is an increased vagal response with vasodilation in the gastrointestinal tract. This may be due to release of vasoconstrictory tone or from bradykinin production in some of the intestinal glands.

F. The Pulmonary Vasculature

Finally, the pulmonary vasculature must be considered separately because of its uniqueness and non-involvement in the systemic vascular reflexes. The resistance of the pulmonary vessels is quite small compared to the systemic circulation (there is the same blood flow, but the pressure gradient may only be 20-30 mm Hg). The pulmonary arteries are normally thin muscular vessels with relatively large luminae. Because of this small gradient of pressure, any change in pulmonary venous pressure will result in a corresponding change in pulmonary artery pressure.

There are several theories regarding the changes in pulmonary vessels:

1. The "passive bag theory" of pulmonary function states that changes in pulmonary artery pressure are caused only by changes in right ventricular output and left atrial pressure. During inspiration, the pulmonary vessels lengthen which would tend to increase vessel resistance. But with the increase in right ventricular output, there is distension of the pulmonary vessels so that the pulmonary artery pressure remains constant. As cardiac output increases, pulmonary artery pressure remains constant until about 16 L/min, after which further increases may cause a slight rise in pulmonary artery pressure. Adrenaline will cause an increase in pulmonary artery and vein pressure but this is not thought to be due to any direct effect on pulmonary vessels but possibly resulting from the effects of the heart.

2. There are however, both sympathetic and parasympathetic nerves associated with the pulmonary vessels. Injection of noradrenaline into one lung before injection of a plastic material will demonstrate vessel constriction in that lung.

3. Hypoxia is known to cause vasoconstriction. This may be the reason for shunting of blood from poorly aerated alveoli. This is probably a local effect for it is observed even with total sympathectomy. Similarily an increase in H^+ concentration and pCO_2 will cause vasoconstriction. If these are local effects, the explanation for why they are opposite to the local effects on the systemic vessels is not known.

4. An increase in pulmonary vein pressure results in capillary distension and pulmonary edema. However, there seems to be a reflex arterial constriction which increases pulmonary artery pressure and minimizes the pulmonary edema. This is similar to the myogenic theory that explains the venous-arteriolar reflex in systemic vessels.

5. It has been shown that serotonin causes some pulmonary vasoconstriction.

In spite of its apparent simplicity, the peripheral vascular system is not just a passive set of tubes but an active system serving the important function of maintaining the normal internal environment.

Experimentation is presently being carried out and will likely bring added knowledge, particularly in the areas of:

—how the cerebral cortex and hypothalamus are affected and how these areas cause changes in the vascular system;

—how local metabolites and hormones affect the normal physiology of vascular smooth muscle to cause constriction or relaxation; and

—how the normal physiology is altered in certain abnormal states such as shock or primary hypertension and how these may be treated;

for there is still much to be learned about peripheral vascular resistance and blood flow.

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Sludging Of Blood – The Brave New World Of The Microcirculation

N. D. Colapinto 6T7

I THE MICROCIRCULATION

The microcirculation refers to the flow of blood through those vessels which are too small (less than 120 microns in diameter) to be seen with the naked eye. These vessels make up by far the greatest proportion of the cardiovascular system both in length and in surface area and supply every living tissue. It takes little imagination to realize that any phenomenon that affects blood flow in these vessels will produce a profound effect on the body in general.

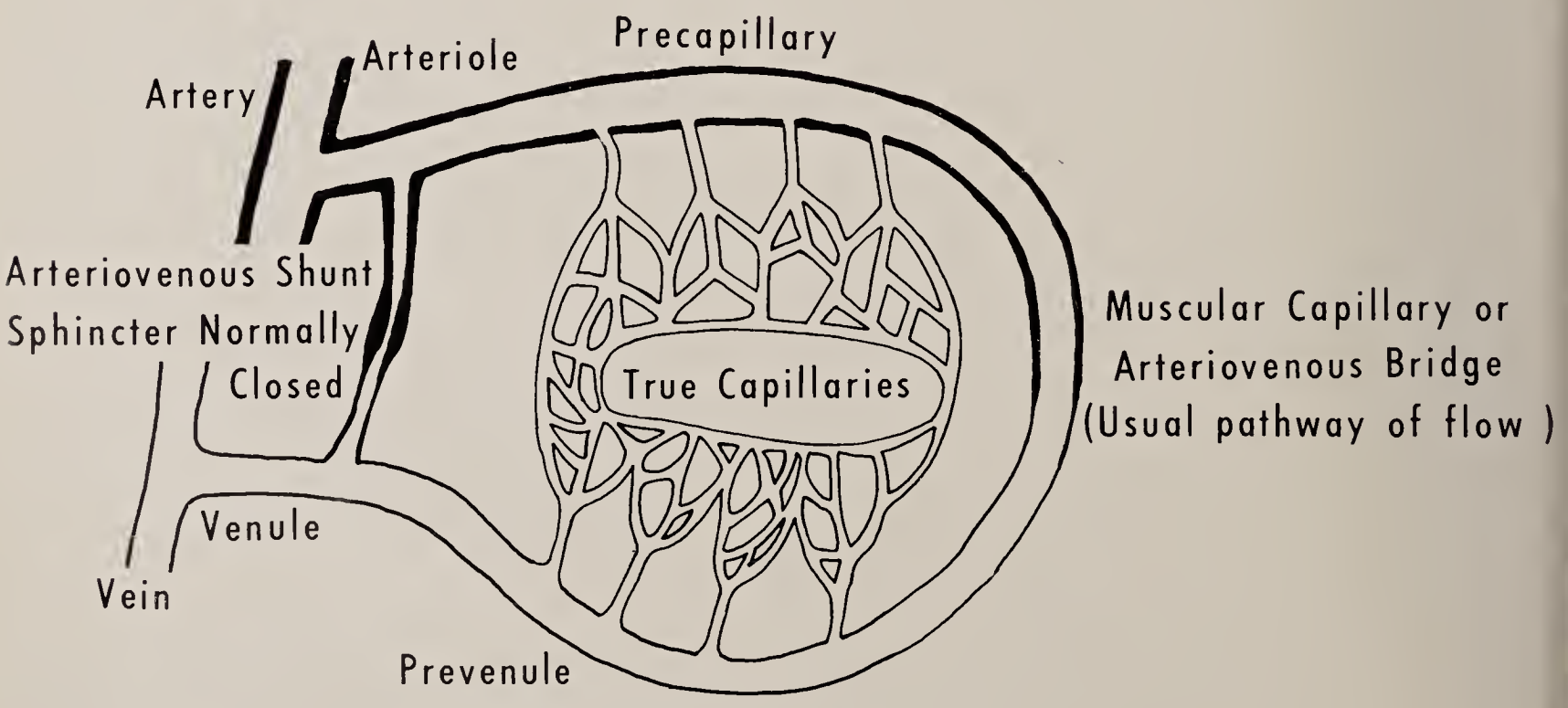
There are three channels of blood flow through the microcirculation (see accompanying figure):

(i) *The arteriovenous bridges* or muscular capillaries. These now are believed to be the main flow pathway under normal conditions.

(ii) *The true capillaries.* These come into use only when extra strain is added to the organ.

(iii) *The arterio-venous shunts.* These are situated proximal to the capillary beds and are normally closed but come into use to divert the blood from the capillary beds of non-vital organs to the brain and heart when the circulation to these organs is threatened as in hemorrhage and myocardial failure. They also serve as an alternative pathway when the capillaries are blocked. Blood flowing in these shunts poorly supplies the tissues and necrosis will eventually result if they are employed as the primary pathway for a prolonged period.

Little study had been done concerning the microcirculation until recently with the development of new microscopic techniques. Animal tissue preparations which have been used include the rabbit ear window, the rat mesentery and hamster cheek pouch. These preparations are observed microscopically under direct illumination or preferably using the quartz rod technique. These methods are not perfect because of the care required to prevent trauma to the tissue while preparing it and the problems of keeping the tissue viable while observing it over a period of time. The need for surgical preparation makes these techniques impractical for observation in humans. But, for this purpose the scleral conjuctiva makes an excellent preparation. Using an ordinary micrscope and an oblique source of light the conjuctival vessels of anesthetized



Diagrammatic Representation of the Microcirculation

humans can be used for observation of the microcirculation. For a routine examination, a clinician may observe the microvasculature easily and rapidly with his ophthalmoscope focused on the conjuctival vessels.

II SLUDGING

Knisely originally coined the term "blood sludge" to refer to an abnormally slow, porridge-like flow of blood that occurred in the small vessels and that was associated with an aggregation of red blood cells. The term now has come to mean simply an abnormal flow through the microvasculature. The differences between sludging and normal flow are detailed in the accompanying table.

(i) *Causes of red cell aggregation.* Erythrocytes normally have a negative surface charge and therefore repel each other. Any factor which influences this charge favors aggregation. One such factor appears to the alteration of plasma protein concentrations in various diseases. In response to infection of the body by microorganisms, there is an increased production of protective immune globulins. The erythrocytes in infection have been examined by the electron microscope and have been found to be covered with a thin protein coat. This protein coat causes the red cells to stick together and clump in the circulation, and causes more rapid precipitation in the test tube. An elevated erythrocyte sedimentation rate (ESR) in vitro, and sludging of blood in vivo are indicators of this process. Similarily in any disease with a high globulin level there will be an elevated ESR and sludging. This includes all infections, all immune disorders including the autoimmune disease, all combinations in which there is considerable tissue necrosis (eg. myocardial infarction, liver cirrhosis) and various cancers. In a similar fashion, an elevated plasma fibrinogen level has been shown to cause coating of the red cells resulting in an elevated ESR and sludging. In contrast, a high albumin level favors break-up of the red cell aggregates.

(ii) *Effects of dextran and low molecular weight dextran.* Dextran is a polysaccharide obtained from the metabolism of sucrose by a bacterium, Leuconostoc mesenteroides. The native material has a high molecular weight (like that of fibrinogen) and causes marked aggregation of erythrocytes. If this material is hydrolysed to a molecular weight of less than 60,000 (like albumin) it causes dissolution of previously formed aggregates. This is the substance known as low molecular weight dextran (Rheomacrodex) which is now in general use. Its effects are due to:

a) increasing the circulating blood volume by increasing the osmotic pressure of blood. This results in a decreased hematocrit and a lowered plasma protein concentration which decreases the tendency to aggregation.

b) increasing the negativity of the red cells. (This is only theoretical.)

c) breaking up the protein coating of aggregated cells. The mechanism of this disintegrating action appears to be that of entering the surface material and reducing the bonding forces.

III CLINICAL APPLICATIONS

The phenomenon of sludging has the following damaging effects upon the body:

(i) The resistance of sludged blood in the circulatory system reduces the rate of blood flow through the tissues. The consequences of this are: a) the production of local tissue hypoxia and b) the production of endothelial hypoxia which leads to increased capillary permeability. If large and rigid enough to block the microvascular bed, sludges can cause death in a few hours by producing anoxia of all tissues supplied by these blocked end organs.

(ii) Agglutinated red cells are ingested and destroyed by phagocytosis in the liver and the spleen. This is probably a major factor in the production of many anemias.

TABLE: FLOW OF BLOOD THROUGH THE MICROVASCULATURE

	NORMAL FLOW	"SLUDGING"
Rate of Flow	Flow is so rapid that individual red cells cannot be seen.	There is a great slowing of the rate of flow.
Red Blood Cells	Red cells flow through the microvessels in a discrete fashion and appear to repel each other slightly. Red cells pass through the capillaries in single file and even then it is such a tight fit that they are deformed during passage.	There is aggregation and clumping of red blood cells. This seems to be one of most important factors in blood sludging.
White Blood Cells	No white cells stick to the inner surface of the vessel walls.	White cells roll along the vessel wall and then gradually stick to its inner surface.
Blood Fluid	No fluid leakage.	Leakage of fluid into the surrounding tissues.
Vessel Walls	The walls are constantly constricting and dilating (vasomotion).	There is spasm of the vessels with resultant blood stasis.

(iii) There is a sedimentation of masses of agglutinated blood cells out of the moving plasma during life. The consequences of this are settling out and cementing together of cells in horizontal vessels leading to venous thrombi and pulmonary embolism.

(iv) There is evidence that various degrees of reduction in the circulating blood volume caused by the above factors initiate prolonged intermittent obstruction of the arterioles of non-vital organs.

These four pathological processes involved in sludging may therefore be involved in many disease states:

1. *Trauma.* When mechanical trauma is applied to the capillary bed under observation, white cells are seen to roll along the endothelium and finally adhere to it. Red cells enter the traumatized area as discrete entities but leave in aggregations or clumps. The flow through the capillaries becomes slow and eventually ceases. This results in anoxia of the capillary endothelial cells which allows leakage of protein and fluid. The A-V shunts now open up so that blood flow through the area continues. But the vital function of nourishment of the part is interfered with because the true capillaries are blocked.

If the microcirculation is observed at a point remote from the traumatized area one notices that the circulation to this normal part soon becomes altered and sludging appears. Clumps of red blood cells, presumably originating from the area of trauma, act as minute emboli and partially block the capillary bed under observation. With severe trauma the red cell emboli become so large that the terminal arterioles may be completely occluded. This produces more extensive capillary stasis and edema and a larger amount of blood bypassing the capillaries through the A-V shunt. This migration of sludge emboli from the locally traumatized area to remote capillaries throughout the body is quite significant. We know that severe trauma (eg. crush injury of the thigh) leads to a tremendous decrease in plasma volume even to shock levels. Fluid is lost from disrupted vessels and from intact vessels in the areas which are blocked by sludges. Generally the amount of fluid required to replace the deficit is in excess of the most generous estimate of the amount of fluid which can be lost in the area (in this case the crushed thigh). This discrepancy can be explained by the fact that sludge emboli originating in the injured area are showered throughout the general circulation. Thus there is blockage of all the microvessels and subsequent exudation into all body tissues. Since every square centimeter of the body is supplied by a network of capillaries one can easily visualize the large total fluid loss that would occur from even minor exudation at each of these tissues.

In burn trauma the same series of events occurs as in the mechanical type. There is still controversy as to whether compression dressings should be used on extensive burns or indeed whether the burn should be dressed at all. If the hypothesis of sludge emboli is true, it probably makes little difference what dressings are used because a more significant amount of fluid is lost remote from the burn site than would be saved by dressing the wound.

2. *Shock.* In hemorrhagic shock there is a decreased circulating blood volume, with the autonomic nervous system causing reflex spasm of the microvessels in the peripheral capillary beds. The current concept is that if this constriction is prolonged the peripheral tissues become irreversiby hypoxic and the patient will inevitably die. Sludging does not occur in hemorrhagic shock. For septic shock, the explanation for the hypotension has been bacteriogenic vasodilatation resulting in decreased peripheral resistance. But now many believe that vasodilatation is not the primary pathology and, if it occurs at all, is probably in the early stages. They feel that vasoconstriction with decreased tissue flow is a more likely cause of irrersibility. By mechanisms previously mentioned, micro-embolization could explain a fluid loss with subsequent hypotension and vasoconstriction, and eventual irreversibility.

It is possible to utilize our knowledge of sludging to provide the rationale in the treatment of all types of shock:

a. Vasopressors actually increase stasis and sludging and therefore aggravate tissue hypoxia. They probably have no place in the treatment of shock except on a short term emergency basis or when administration of fluids would aggravate pre-existing cardiac failure following a coronary thrombosis. Even in these cases, vasopressors which also have a cardiotropic action are preferred.

b. Vasodilators open microvessels and favor decreased sludging and increased flow and are therefore of theoretical benefit in traumatic or septic shock, but not in hemorrhagic shock where sludging does not occur.

c. Low molecular weight dextran reduces sludging and is therefore also theoretically a good treatment for traumatic or septic shock.

d. Steroids (ACTH and cortisone) break up sludges and this is the possible mechanism of action of these hormones in reducing capillary permeability and vasospasm in traumatic and septic shock.

3. *Anemia.* Many of the "auto-immune" anemias occuring secondarily in various malignancies, the collagen diseases, liver cirrhosis, etc. can be explained on the basis of phagocytosis of agglutinated red cells. The probable mechanism is coating of the red cells by the excess globulins in these diseases. These coated red cells stick together forming clumps which are readily

phagocytosed by the reticuloendothelial cells of the liver and spleen.

4. *Phlebitis.* Thrombophlebitis is a common complication of prolonged bed rest. In predisposed patients (post-surgical, post-myocardial infarction and post-partum) sludging is a common factor. Experimentally, with loss of suspension stability and accumulation of these heavy clumps of cells (sludges) a settling out occurs in horizontally running venules. This process may extend to the larger vessels causing slowing of flow which is the prime factor in the pathogenesis of phlebitis.

5. *Peptic Ulcer.* Key has shown that stimulation of the vagi in rats also causes sludging in the general circulation. It is tempting to extrapolate from this that constant vagal stimulation in an anxious person causes sludging as well as hyperacidity. These sludges cause stasis in the microvessels of the gastric mucosa producing malnourishment of this area with a resulting decrease in local tissue resistance or even necrosis. The high acidity (or even normal acidity in the case of gastric ulcers) then acts upon the vulnerable mucosa to produce ulceration. Utilizing this theory, the association of the gastro-intestinal ulceration with severe burns (Curling's ulcer) is easy to explain.

6. *Atherosclerosis.* There are examples of chronic metabolic diseases which are associated with both chronic sludging and atherosclerosis, eg. diabetes mellitus. A possible explanation is that the sludges produced in these diseases block the capillary beds of the vasa vasorum of the aorta and other large arteries. This would cause hypoxia and decreased resistance of the vessel wall to lipid infiltration. We also know that women are protected from atherosclerosis during their reproductive years and that estrogenic hormones apparently decrease sludging.

7. *Cancer.* Three interesting features of cancer may be explained by sludging: (i) Trousseau's sign. The occurrence of migratory thrombophlebitis is cancer of the pancreas and other neoplasms can be explained by sludging in the veins. (ii) Anemia. This can be explained by phagocytosis of the sludges by the R.E. system. (iii) Cause of death. It is possible that sludge emboli slowly choke off each of the capillaries of the body in turn producing gradual deterioration and eventual death.

8. *Collagen diseases.* The varied manifestations of the collagen diseases such as edema, anemia, skin rash and vascular involvement can be explained on the basis of sludging.

9. *Lethal radiation.* It is a distinct possibility that the adverse effects of a lethal dose of radiation are due to the fact that high doses of radiation produce sludging of blood.

10. *Psychiatric disease.* One cannot help but wonder about the possible effects of chronic sludging and microembolization in the brain with resultant cerebral edema. Many of the manifestations of mental diseases such as irritability, confusion and euphoria are also manifestations of anoxia caused by breathing an atmosphere low in oxygen. It would be interesting to see the results of a study of the bulbar conjunctiva in mental illness.

11. *Aging.* With increasing age there are changes in skin texture, arterial elasticity, muscle tone and the production of atherosclerosis. Aging could be due to intermittent bouts of sludging occuring throughout life producing intermittent tissue hypoxia which leads to degeneration of cells.

Since sludging is observed in all these conditions and many more, it is certainly tempting to assume that sludging is responsible for many of the manifestations of disease. Further, if an agent which prevented sludging could be discovered and could reverse the manifestations of these diseases it would be an incredible boon to medicine. This is an exciting and provocative field which although hypothetical has its basis in factual laboratory experimentation and clinical observation. The natural reaction is to reject such obvious and simple explanations for problems of such magnitude. But one must admit that it is an intriguing theory and of such potential medical significance that it deserves investigation.

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Venous Thrombosis In The Lower Extremities

J. E. Dixon 6T7

In approximately forty per cent of routine autopsies the pathologist finds evidence of significant antemortem venous thrombosis of the lower limbs. This high incidence indicates that this is one of the commonest conditions with which physicians and surgeons must deal. This article will discuss various aspects of venous thrombosis in the lower extremities. First, it will define terms used, then it will discuss the pathogenesis, etiology, clinical picture, complications and treatment. Finally, it will mention the association of thrombophlebitis with malignancy.

I Definition of Terms

A *thrombus* is a solid mass or plug of blood constituents formed in flowing blood. Initially, it consists of platelets adhering to one another and to the vessel (or heart) wall, but later it includes blood cells and fibrin.

A *clot* is a solid mass or plug of blood constituents formed in static blood as a result of the conversion of soluble plasma fibrinogen into almost insoluble fibrin through the ordinary process of coagulation.

An *embolus* is the impaction in some part of the vascular system of an insoluble material brought there by the blood stream.

Phlebothrombosis is a condition in which thrombosis occurs in a vein which is free from inflammation at the time of thrombosis.

Thrombophlebitis is a condition in which thrombosis develops secondary to inflammation of the vein.

II Mechanism of Thrombus Formation

When a vessel is injured, the endothelial cells are lost or separated, the subendothelial tissue is exposed, and adenosine diphosphate (ADP) is released. As phatelets in the blood stream come in contact with and adhere to collagen of the exposed subendothelial tissue, a chain reaction begins which leads to the formation of a thrombus. ADP released from the injured cells in the area and also from the adherent phatelets appears to stimulate phatelet aggregation. As a result, an unstable "platelet thrombus" forms. Materials released at the site of injury and from the phatelets (e.g. phospholipids) together with the ADP stimulate and accelerate fibrin formation. The fibrin surrounds and stabilizes the platelet aggregate forming a "white thrombus".

The size of the platelet-fibrin mass will vary with the extent of vessel damage, the rate of blood flow, and the concentration of factors which neutralize the action of ATP. If the blood flow is rapid, phatelets are more easily swept away and the coagulation-promoting materials may be diluted and neutralized, thus limiting the size of the thrombus. If blood flow is slow, as in a vein, fewer platelets are swept away, and an occlusive mass may develop. If this happens, a static column of blood forms distal to the obstruction. Here, coagulation factors have a longer time to act, and they form a mass of coagulated blood, a "red tail", which adheres to the "white thrombus".

The fate of the thrombus is variable. It may disintegrate because of ADP degradation in the case of the "platelet thrombus" or by fibrinolytic action on a "white thrombus". In other instances part or all of the thrombus may break off to form an embolus, or, the thrombus may be incorporated into the vessel wall with re-canalization by endothelial tissue.

III Etiology of Venous Thrombosis

The etiology of venous thrombosis is still a controversial matter. Certain factors related to the vessel wall, the blood components, and blood flow influence its formation.

A. *Vessel Wall Factors*

A thrombus does not usually form in a normal vessel. An abnormal endothelial surface may be due to intrinsic and extrinsic factors. Intrinsic factors include: a) vessel disease such as acute phlebitis, phlebosclerosis, radiation damage, pre-existing thrombophlebitis, b) anoxia from venous stasis due to incompetent valves, varicose veins or local obstruction, c) an alteration in surface charge of the vessel wall.

Extrinsic factors include prolonged pressure on a vein from bed rest or an adjacent tumor, and a crush injury such as may occur with a fractured femur.

B. *Blood Component Factors*

Platelet factors may stimulate thrombus formation when there is an increased number of platelets which may occur post operatively, post partum, and with infections (pneumonia, rheumatic fever) or when there is an increased platelet adhesiveness as in infections, with release of ADP, in pregnancy, post partum, or with ischemic heart disease. Increased serum levels of certain proteins (fibrinogen, antiplasmin), saturated fatty acid and phospholipids, and epinephrine; or decreased levels of antithrombin will affect platelet aggregation and fibrin formation.

Red blood cell factors may lead to thrombus formation by red cell injury or hemolysis which may cause

release of ADP, or by sludging in conjunction with a relative or absolute increase in the number of red blood cells (e.g. primary or secondary polycythemia, dehydration, certain malignancies or abnormal red cells such as sickle cells.

C. *Blood Flow Factors*

Disturbed flow or eddying may increase the possibility of thrombus formation by causing more platelets to come into contact with the vessel wall, and by damaging the vessel wall and blood constituents. Eddying may occur at natural irregularities such as the junction of vessel branches, the site of valves, or areas where the vessel is constricted such as the inguinal ligament, the origin of the soleus muscle or areas of vessel dilatation such as varicose veins, venous sinuses.

Slow blood flow will favour thrombus formation by allowing time for more platelets to aggregate, and more fibrin to form, and by causing fewer platelets to be swept after aggregation. Blood flow may be reduced by low cardiac output as in arteriosclerotic, rheumatic or hypertensive heart disease; increased blood viscosity e.g. dehydration, myeloproliferative disorders; decreased body activity e.g. bed rest. Local causes include pelvic surgery and raised intra-abdominal pressure as in abdominal tumors, pregnancy, ascites, obesity.

All of these factors can influence thrombus formation in any part of the cardiovascular system, but there are several reasons why thrombi develop more commonly in the venous rather than the arterial system. In veins blood flow is slow and uniform rather than pulsatile, it is often arrested locally for considerable periods of time, and blood flows from small to larger vessels. The veins are thinner walled and lie more superficially, and thus are more affected by trauma than are arteries. Nascent thrombi are less easily dislodged from a vein because the vein wall does not expand with each beat. Finally, the physical properties of the venous and arterial blood are different. The hematocrit is increased with the loss of tissue fluid, and possibly, there are different coagulative properties after passage through the capillary bed.

IV Clinical Presentation

Many cases of venous thrombosis are not diagnosed until post mortem examination because frequently during life there are no signs or symptoms or, they may be too minimal to be noticed by the patient or the physician. The usual sites of thrombus formation in the lower limb are the plantar veins, the veins of the soleus and adductor muscles, and the deep veins of the thigh and pelvis. The valve pockets are a common focus for initiation of the thrombus. The left leg is more frequently affected than the right, perhaps because of the longer and more oblique course of the left iliac vein as it crosses over the spinal column to empty into the inferior vena cava.

The signs and symptoms vary with the functional importance of the area drained by the affected vein, the rapidity and extent of thrombus formation, the collateral circulation of the area, the associated disease, and with the degree of vessel wall inflammation. The patient with phlebothrombosis may complain of mild unilateral pain and stiffness in the calf, particularly on active motion. This pain can often be demonstrated by passive dorsiflexion of the ankle (Homan's sign). There may be mild to moderate swelling of the foot, calf, or thigh, with edema and congestion of the surrounding muscles, dilatation of the superficial veins, and occasionally, local cyanosis. There may also be a tachycardia and a low grade fever. In superficial thrombophlebitis, which most commonly involves the superficial saphenous vein, there is tenderness, erythema, heat and pain along the course of the vein. Occasionally, cellulitis and deep thrombophlebitis may complicate the picture. In deep thrombophlebitis, the patient may experience severe pain, stiffness and tenderness in his leg. Signs of inflammation can usually be demonstrated; heat, erythema, pain, swelling, and, rarely, some loss of muscle function. If there is considerable venous obstruction, the leg will be swollen, cyanotic and cool. There is usually a slightly elevated body temperature, tachycardia greater than can be explained by the degree of pyrexia, and a polymorphonuclear leukocytosis.

In an occasional postoperative or postpartum patient, there is an acute massive involvement of the common femoral veins with reflex arterial spasm. This condition is known as phlegmasia alba dolens and presents as a pale, edematous, very painful leg. If the process continues on to involve the iliac venous system with severe arterial spasm, a dusky purple, gangrenous, edematous, excruciatingly painful leg, will develop sometimes associated with shock and death. This is known as phlegmasia caerulea dolens.

V. Complications

There are early and late complications of venous thrombosis. The chief concern with deep venous thrombosis in the leg is the development of pulmonary embolism. In thrombophlebitis, the thrombus is more adherent to the vessel wall than in phlebothrombosis because of the inflammatory reaction, however, it still may be dislodged. There is a high occurrence of pulmonary embolism secondary to silent venous thrombosis. Most cases of thrombophlebitis are aseptic, but if infection occurs, septic thromboembolism may follow. Phlegmasia alba and caerulea dolens are other early complications of venous thrombosis.

Late complications include the development of secondary varicose veins, valve incompetence, phlebosclerosis, and the post phlebitic syndrome. In this syndrome there is a feeling of heaviness in the leg, edema that remains constant or increases, local temperature elevation, local colour changes, a brownish pigmentation

over the internal and external malleoli, tenderness over the same area, muscle atrophy, and areas of stasis dermatitis and skin ulceration which may develop ten or fifteen years after the thrombosis.

VI Management

Prophylactic measures form an important aspect in the management of venous thrombosis. These measures attempt to minimize the etiological factors of thrombosis, and should be carried out on postoperative and postpartum patients, and on any person, especially the elderly, who must have long term bed care. These persons should have a good nutritional diet, a well maintained fluid balance, and a normal hemoglobin level. Cases of cardiac failure and hypotension should be treated. Infections should be prevented, but if they develop, they should be treated vigorously. Obese patients should be encouraged to lose weight. Venous stasis in the legs can be controlled by a ten degree elevation of the legs, leg exercises, a ripple mattress, early physical activity and mobilization. Sometimes elastic bandaging of the legs from the toes to the thighs may be necessary.

When deep venous thrombosis does develop, the patients should be put to bed, his legs immobilized and elevated ten to fifteen degrees, with light bandaging and with local heat applied to the affected limb. He may be allowed up with leg bandages on, one or two days after all local signs have disappeared.

The ideal drugs for treatment would prevent platelet adherence and aggregation, prevent formation of or destroy ADP, and stimulate fibrinolysis and disruption of platelet aggregates. At present, drugs which are less than ideal must be used.

1. Anticoagulants in the usual doses, are ineffective in preventing initial platelet aggregation, but suppress thrombus growth and stabilization. *Heparin* (given intravenously) acts a) to prevent formation of thromboplastin from platelets and plasma factors, b) as antithromboplastin, to prevent conversion of prothrombin to thrombin, c) as antithrombin, to block conversion of prothrombin to thrombin, and d) to activate serum lipase. Thus heparin delays or prevents coagulation, but only in very high doses can it block the effect of ADP on platelet aggregation. *Dicumarol* (given orally) decreases coagulation factors II (prothrombin), VII, IX, and X by competitive inhibition of vitamin K which is used by the liver to produce these factors. However, as these factors are already present in the blood, dicumarol requires a few days to become effective, and so heparin and dicumarol are both administered until prothrombin levels reach ten to twenty per cent of normal, which is usually in two or three days. Then heparin is discontinued, and the dosage of dicumarol is adjusted to maintain this prothrombin level. Anticoagulant therapy is continued for three to six weeks after all signs and symptoms of the disease have disappeared.

2. Fibrinolysins have been given enthusiastic experimental trials. Plasmin is unable to penetrate the fibrin around the thrombus, and so is ineffective. Streptokinase and urokinase which activate the plasminogen within the thrombus to form plasmin, can penetrate into the thrombus. Their use, however, is still limited to investigation.

3. Anti-inflammatory drugs. The pyrazole drugs such as phenylbutazone, inhibit thrombus formation in flowing blood by suppressing platelet-collagen interaction. These drugs are used for cases of superficial thrombophlebitis.

4. Antibiotics are occasionally used in thrombophlebitis if bacterial infection is suspected.

5. Low Molecular Weight Dextran (Rheomacrodex) is thought by some to prevent thrombosis by coating the red cells and the intima with a negative charge, thus counteracting red cell aggregation and lowering blood viscosity.

6. Surgery is sometimes used to prevent the complications of thrombophlebitis. A vein between the thrombus and the pulmonary circulation may be ligated. Thrombectomy may be done if the thrombus is detected early and if it is of significant size. Stripping or ligation of varicose veins will help to prevent further thrombosis in the damaged vessels. Finally, in the postphlebitic syndrome, the fibrotic and ulcerated areas of the lower limbs may be resected.

VII The Relationships of Thrombophlebitis to Cancer

Thrombophlebitis may occur as a systemic manifestation of malignant disease. It has been reported to occur in association with carcinoma of the lung, pancreas, prostate, breast, female reproductive system, and with leukemia. This thrombophlebitis has peculiar characteristics. Usually it involves short segments of the superficial veins of the extremities or abdomen; it may also involve veins in the intestine, kidney, heart, liver, or brain. It migrates from one area to another anatomically unrelated area. Typically, there are long periods of remission with recurrences at intervals of months to years. This form of thrombophlebitis is particularly resistant to the usual forms of treatment, especially dicumarol therapy.

There are various theories as to the etiology of the thrombophlebitis;

1. Thrombosis in the region of the tumor may be caused by tumor compressing or invading the vein wall. This would damage the wall and cause a reduced blood flow.

2. Blood-borne tumor metastases may give rise to platelet thrombi at the site where the tumor cells lodge.

3. There may be a hypercoagulable state produced by thromboplastic, proteolytic, or fibrinogen-like substances released by the malignant tissue or the damaged adjacent tissues. Release of trypsin from the panreas may account for the thrombophlebitis found in carcinoma of this organ.

A migratory thrombophlebitis will occur not only in association with malignant disease, but also with polycythemia rubra vera, certain hemoglobinopathies, thromboangiitis obliterans, ulcerative colitis, secondary syphilis, and some of the collagen vascular diseases.

If a physician is presented with several occurrences of thrombophlebitis which fail to respond to standard therapy, he should not only repeat his complete history and physical examination, but also carry out certain special investigations such as chest x-ray, urinalysis, upper gastrointestinal series, barium enema, PAP smear or sigmoidoscopy.

There is still much to be learned about venous thrombosis, its pathogenesis, complications, and management. Close attention must be paid to future experimental and clinical work which may provide a better understanding of thrombus formation. This, coupled with improved physical and chemical inhibition and control of thrombosis should lower the present morbidity and mortality of this condition.

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Atherosclerosis - Some Mechanisms Involved

INTRODUCTION

Atherosclerosis is the commonest and most important disease of the arteries. It is a type of arteriosclerosis affecting large and medium-sized arteries. Pathologically it is characterized by an "atheroma" or an accumulation of lipids, blood products, fibrous tissue and calcium within the arterial intima.

To date the underlying etiology of atherosclerosis is not known. Past and present research has implicated a myriad of factors which seem to be associated with atherosclerosis but no causal links have been found. Some of these factors include genetic constitution, age, sex, level of serum cholesterol, hypertension, obesity, and smoking.[4] Insofar as the lipid fraction of the atherosclerotic plaque is the most significant and the intima is invariably involved, it is likely that the primary etiology of atherosclerosis will be explained by abnormalities found either in lipid metabolism or in changes in the vessel wall. Some experimental results point to disturbances in lipid metabolism leading to deposits of lipoid substance in the arterial wall, while others incriminate intrinsic wall defects with resulting lipid deposition.

The three types of plasma lipids involved in the process of atherosclerosis are neutral fats, phospholipids, and cholesterol. Neutral fats are composed of esters of fatty acids and glycerol. These are mainly triglycerides with three fatty acids attached to glycerol. The normal range is 40-60 mgm%. Phospholipids are fats containing phosphoric acid and a nitrogenous base, with lecithin, sphingomyelin, and cephalin being the principal compounds concerned. The normal range is 150-280 mgm%. Cholesterol represents hydrogenated phenanthrene derivatives. Seventy per cent is esterified with fatty acids and the remainder circulates in a free form. Here there is significant variation in plasma levels with diet, age, sex, race, physical activity, occupational stress, and geographic locale. Friedberg considers a value greater than 260 mgm% in a person over age 50 to be abnormal.[4] The total blood lipid is 700 mgm per 100 ml. of which 32% is neutral fat, 35% is phospholipid, and 33% is cholesterol. There are three mechanisms for transporting lipids: (1) Neutral fats are transported as a suspension in plasma. They can be either microglobules or chylomicrons. (2) Lipids can combine with proteins to form a soluble lipoprotein complex. Basically there are two types, alpha and beta, corresponding to whether an alpha or a beta globulin is involved. The beta lipoprotein fraction comprises most of the serum lipid and transports 70-90% of serum cholesterol.[9]

The arteries are nourished by blood from the lumen and if the walls are thick enough by vasa vasorum. The blood contains cholesterol and other lipids. Some of the cholesterol fraction may be retained and deposited while the rest of the plasma is filtered through the wall and reabsorbed by the adventitial lymphatics. To have lipid deposition we can postulate an increased filtration presenting the intima with a greater load than it can handle or a decreased transarterial diffusion due to a structural or metabolic defect in the wall. Three important aspects of this problem and of current research will be evaluated:

—the plasma content of lipids and lipoproteins and their physicochemical characteristics

—mechanical factors which promote filtration through the wall

—the structure and function of the arterial tissue, especially the intima.

THE PLASMA LIPIDS

(i) *Hypercholesterolmeia.* The importance of increased serum cholesterol levels resulting in increased intimal deposition of cholesterol is one of the most controversial topics in assessing the etiology of atherosclerosis. Clinical evidence shows that conditions such as diabetes mellitus, xanthomatosis, hyothyroidism, and nephrosis in which an elevated serum cholesterol level is found predispose to atherosclerosis. Diet is one of the main factors associated with hypercholesterolemia. There are two sources of cholesterol—exogenous and endogenous. The exogenous or dietary intake is usually between 200 and 800 mgm. per day. The endogenous capacity or ability of the body to manufacture cholesterol is 2.5 to 3 grams per day. Furthermore, there is a reciprocal relationship between these two sources, i.e. the more exogenous cholesterol received from the diet, the less endogenous cholesterol produced. As a result reducing the dietary intake does not necessarily lessen the plasma levels. On the other hand increasing cholesterol levels in the diet has been associated with elevated serum levels.[4]

(ii) *The cholesterol-phospholipid (C/P) ratio.* This ratio is regarded as an index of the stability of lipid

solutions.[1] Phospholipids are bound to beta globulins. Cholesterol is also transported bound to beta globulins. probably at a different site from the phospholipids and it follows that the more phospholipids present bound to beta globulins the more cholesterol can be bound and maintained in solution. Cholesterol itself is insoluble in aqueous solution and requires this binding to be maintained in solution. Hence if the C/P ratio increases there will be deposition of cholesterol. Of the two lipoprotein fractions, beta carries the bulk of total cholesterol (70 - 90%). The alpha fraction is highest in the young, decreases with age, and is increased in premenopausal women.[11 14] This may help explain the sex incidence of atherosclerosis. In addition the alpha C/P ratio is 0.5 and the beta C/P ratio is 1.0[4], hence leading to a greater cholesterol deposition.

(iii) *Hormonal factors.* Several hormones have been shown to have some control over plasma lipids levels. It has previously been stated that the incidence of atherosclerosis is lower in women. Estrogen is believed to decrease the cholesterol level and the C/P ratio.[3] In support of this theory figures have been published demonstrating an increased incidence of atherosclerosis in bilaterally oopherectomized and postmenopausal women,[15] and a decreased incidence in men treated with estrogen for cancer of the prostate.[13] In hyperthroidism the intestinal excretion of cholesterol is increased and this may depress serum levels.[4] Adrenal cortical hormones increase serum cholesterol levels, most likely through an increase in fat mobilization.

(iv) *Plasma foam cells.* Macrophages in the liver and the reticuloendothelial system take in cholesterol and become foam cells. These enter the circulation, penetrate through the spaces between the endothelial cells,[5] and disintegrate, releasing their lipid contents.[10] The cholesterol is treated as a foreign body and promotes secondary fibrosis and vascularization.

MECHANICAL FACTORS

One of the difficulties in trying to establish the etiology of atherosclerosis is to explain the definite predilection of certain sites in the early stages of atherosclerosis. Any part of the aorta and other musculoelastic vessels could theoretically by a site for atherosclerotic change, yet the posterior wall of the descending aorta, bifurcation of the aorta, and bends in the coronary and cerebral arteries seem to be sites of predilection.

(i) *Pressure.* The pressure in the arterial system seems to be one of the factors involved in atherosclerosis. Undoubtedly it helps perfuse the vessel walls and while doing so may drive in an excess of lipids.

(ii) *Turbulence and intimal damage.* At the sites of predilection cited above there are turbulences in the normally streamline flow of the blood and the effects of turbulent flow will be increased in hypertension. There are many colloid particles suspended in the plasma and under conditions of local turbulence or inflammation they may precipitate out as an intimal film. This impairs the nutrition of the vessel with resulting subendothelial-intimal anoxia and increased permeability, infiltration, and deposition of cholesterol.[8] A second mechanism postulates changes in the vessel wall which leads to thrombus formation. These changes may result from trauma, inflammation, or flow effects. The thrombus is then thought to be covered over by a layer of endothelium and incorporated into the wall.[2] Organization of the thrombus leads to fibrous change and formation of the atheromatous plaque.

VESSEL WALL FACTORS

(i) *Intimal capillaries.* Capillaries in the intima may rupture and release red cells which are rich in lipid. These capillaries may be part of the normal nutritional mechanism or may arise in response to early intimal atheroma formation.

(ii) *Vessel wall metabolism.* The vessel wall has been shown capable of synthesizing, accumulating, and removing various substances including lipids.[12] It is possible to have a disturbance in the metabolism of the wall.[7] This could result in a deficiency in the enzymes required to transport substances through the vessel wall and hence lead to the deposition of cholesterol and other lipids in the intima. Intimal foam cells either from the liver or arising in the intima are also implicated in metabolic disturbances since they contain hydrolytic and esterifying enzymes. These enzymes lead to the breakdown of complex substances including engulfed lipoproteins to amino acids, phospholipids, fatty acids, cholesterol, and cholesterol esters. Amino acids and phospholipids are soluble and hence removed. The fatty acids are catabolized to carbon dioxide and water and cholesterol and its esters are deposited in the vessel wall.

(iii) *Mast cells.* Mast cells in the wall contain serotonin and histamine which, when released for as yet undetermined reasons, increase vascular permeability and the accumulation of colloid particles.

PROGRESSION OF THE PRIMARY ATHEROSCLEROTIC LESION

The development of atherosclerosis extends throughout life. The exact processes of progression are not known with certainty and the following is presented as a reasonable mechanism. The deposition of intimal lipid may cause an inflammatory reaction. This results in swelling and if the wall thickens enough its nutrition and oxygen supply are severely impaired and necrosis occurs. Necrosis leads to softening of the tissue and typical atheroma formation (necrotic and degenerative tissue, cholesterol, and other lipids). The atheroma may extend to the endothelial surface and rupture into the lumen resulting in ulcer formation. Calcium is depo-

sited around this focus and in exposed, thickened, fibrous areas of intima resulting in large calcified plaques. Sometimes capillaries in the vessel wall rupture resulting in local hemorrhage and bulging of the plaque into the lumen.

CONCLUSION

In atherosclerosis there is much that is theory, little that is fact. The mechanisms presented in this article represent current trends in our thinking at the present time. It may be that even they are far from the truth. In some centres it is thought that the accumulation of cholesterol and other lipids in the atherosclerotic plaque is secondary or even coincidental to some other primary process as yet completely unknown. Whatever the answer the field remains wide open for basic research.

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Abstracts

Autoregulation of Cerebral Blood Flow

Electromagnetic flow measurements during acute hypertension in the monkey. K. Yoshida, J. S. Meyer, K. Sakamoto, J. Handa. Circulation Research 19: 726-738. Oct. '66.

Changes in blood flow through the internal carotid, vertebral and external carotid arteries were measured by electromagnetic flowmeters during and after acute hypertension induced by closing a clamp around the descending thoracic aorta in anesthetized monkeys. Both carotid sinuses were denervated to eliminate the effect of the carotid sinus reflexes during acute hypertension. There is an autoregulatory process within the cerebral arterial system which tends to maintain constant cerebral blood flow in the face of a sudden increase in blood pressure. The internal carotid and vertebral arterial system showed both rapid and delayed autoregulatory response to rapid increases in blood pressures; the rapid (primary) responses occurred within seconds, the progressive (delayed) within 3-4 min. In contrast, the flow response within the external carotid system appeared to be passive. Cervical sympathetic innervation and myogenic reflexes (Bayliss reflex) both appear to play a part in the rapidly occuring (primary) regulation of cerebral blood flow. The mechanism responsible for delayed and progressive (secondary) autoregulation in the cerebral vasculature appeared to be metabolic, since it was predominantly influenced by changes in blood PCO_2. Changes in intracranial pressure did not seem to be involved in autoregulation.

Detection of Venous Thrombosis in the Human by Means of Radioiodinated Antifibrin-Fibrogen Antibody

T. Reich et al. Surgery 60: 1211-1215, Dec. '66.

A test for establishing the presence of asymptomatic or symptomatic calf vein thrombosis is described. The criteria for clinical diagnosis of thrombosis was calf tenderness or pain in calf on dorsiflexion of the foot with one or more of the following signs: leg edema, dilated superficial leg veins, fever, redness, tachycardia or a palpable cord. The test involves intravenous injection of a radioiodinated horse antibody which can be used for the immunological identification of both human fibrin and fibrinogen. Using a radiation scintillation detector to find localization of I^{131}, symptomatic thrombus in the calf was confirmed and asymptomatic thrombus was recognized up to three days before it produced findings on physical examination. The uptake of I^{131} by the thyroid gland was prevented by using Lugol's solution. The test was not affected by anticoagulant therapy and yielded positive results even in thrombosis which had been diagnosed one week previously.

Student Research

The Effect Of The Hematocrit On Red Cell Injury During Circulation

WITH A DISCUSSION OF THE ROLE OF THE RED CELL IN HEMOSTASIS AND THROMBOSIS

Most investigators have neglected the possibility of a role for the red cell in the processes of hemostasis and thrombosis. This article will review current concepts of these processes and comment on red cell involvement in them. The results of a summer research project dealing with the injurious effects on the red cell of flow *in vitro* will be presented and their significance discussed.

Recent research into the physiology of hemostasis and the patho-physiology of thrombosis, which are two aspects of a single process, has been most fruitful in the areas of platelet fine structure, physiology and biochemistry. Figure 1 summarizes the current concept of the role played by platelets in hemostasis and thrombosis in man.[1-6]

On contact with collagen fibrils present on an injured vascular surface, platelets adhere to these fibrils and undergo a sequence of events known as platelet degranulation. This consists of the loss of intracellular potassium ions with consequent swelling and loss of organelles (lysosomes, mitochondria) and cytoplasmic inclusions (glycogen granules). When platelets degranulate, their adenosine triphosphate (ATP) content decreases and adenosine diphosphate (ADP), serotonin (5-hydroxytryptamine, 5HT), permeability factors (i.e. heat-stable materials which increase vascular permeability) and lysosomal enzymes are released into the surrounding plasma. Furthermore an alteration in the platelet cell membrane allows phospholipids (platelet factor three, PF3) to activate the intrinsic pathway of blood coagulation at the platelet-plasma interface and thereby initiate thrombin production.

ADP released from platelets and, as will be shown later, from other sources causes platelets to stick together or aggregate. *In vitro* studies show that as little as 2.5 nanograms ADP (1 nanogram = 10^{-9} gram) per millilitre plasma will initiate platelet aggregation while 25 nanograms per millilitre provide a maximal stimulus. These concentrations of ADP are within a physiological range. Degranulation, which accompanies platelet adherence to collagen fibrils, does not occur in an *in vitro* ADP-induced aggregation system model which is characterized by only slight swelling of the platelets. Whether or not ADP, serotonin, and permeability factors are released during this ADP-induced aggregation has not been demonstrated conclusively. However PF3 does become available at the platelet surface to activate the intrinsic pathway of blood coagulation.

Thrombin formed as a result of either degranulation or aggregation acts as a positive feedback to cause further platelet degranulation, even at thrombin levels insufficient to cause fibrin formation. Thrombin-induced degranulation is accompanied by ADP release and in turn this induces aggregation. All of the factors released from platelets by collagen fibrils are also released by thrombin. Thrombin also plays an important role in the formation of a thin layer of fibrin over the platelet mass, thus stabilizing the hemostatic plug or thrombus that has been formed.

The structural similarities of a normal hemostatic plug and a thormbus are illustrated in Figure 2. Near the vessel wall, platelets are adherent to collagen, degranulated, and grossly swollen. In the middle of the hemostatic plug and thrombus, platelets are aggregated but intact due presumably to the action of released ADP. At the periphery they are degranulated and swollen presumably by the action of thrombin. The entire mass is stabilized by a thin layer of fibrin.

Various factors limit the extent of or inhibit hemostatic plug formation and thrombosis *in vivo*. These include the normal endothelial surface of vessels which prevents platelet-collagen interaction and plasma enzymes which destroy ADP and (adenosine monophosphate AMP) which in turn inhibits ADP-induced aggregation. Such enzymes include myokinase which converts ADP to ATP and plasma phosphatases. Antithromboplastin and antithrombin are also which involved by their inhibition of thrombin formation and its action. In addition plasmin may destroy any fibrin formed as a stabilizing layer over the platelet mass. These factors are also shown in Figure 1.

The Role of the Red Cell in Hemostasis and Thrombosis

In 1960 Hellen[7] showed that red cells contained a factor that aggregated platelets. Gaarder et al[8] proved that this factor was ADP. Recently Marr et al[9] showed that the ATP content of blood issuing from a severed mesenteric vessel in hamsters decreased to one-sixth its initial value during the first fifteen seconds after the vessel was severed. In the same period the ADP content of the blood rose on an equimolar basis. Since the

STIMULUS:	**COLLAGEN**	**ADP**		**THROMBIN**
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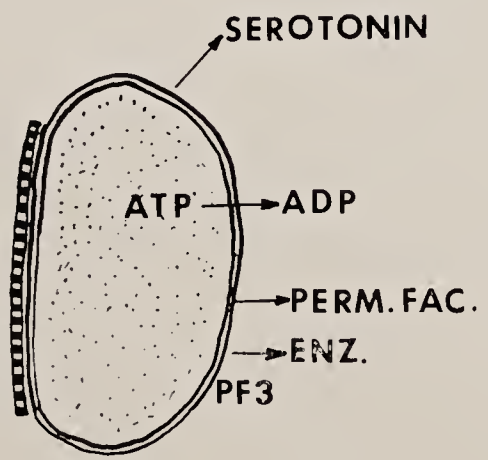
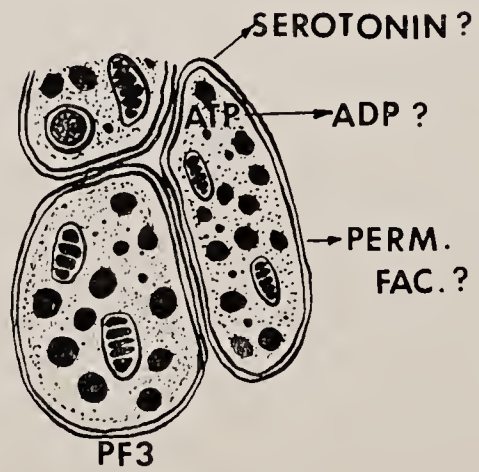
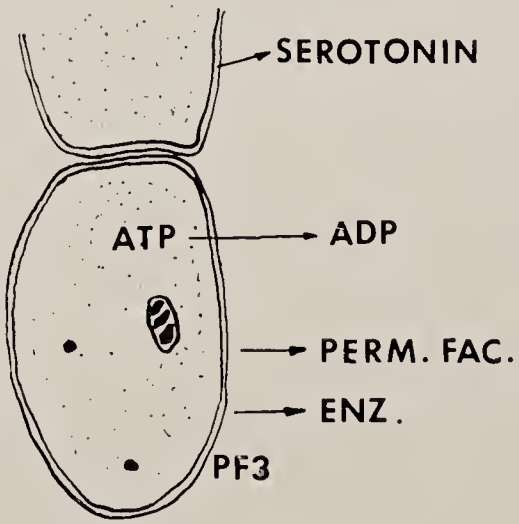
RESPONSE:			i 	ii FIBRINOGEN FIBRIN CAP
	ADHESION AND DEGRANULATION	AGGREGATION	DEGRANULATION AND AGGREGATION	
INHIBITORS:		AMP, ADENOSINE MYOKINASE PHOSPHATASES	ANTITHROMBOPLASTIN ANTITHROMBIN	PLASMIN

Figure 1: Modern concept of the role of platelets in hemostasis and thrombosis in man. ATP = adenosine triphosphate. ADP = adenosine diphosphate. PERM.FAC. = permeability factors. ENZ. = enzymes. PF3 = platelet factor three. Arrows indicate release into the plasma. PF3 is made available at the plasma-platelet interface.

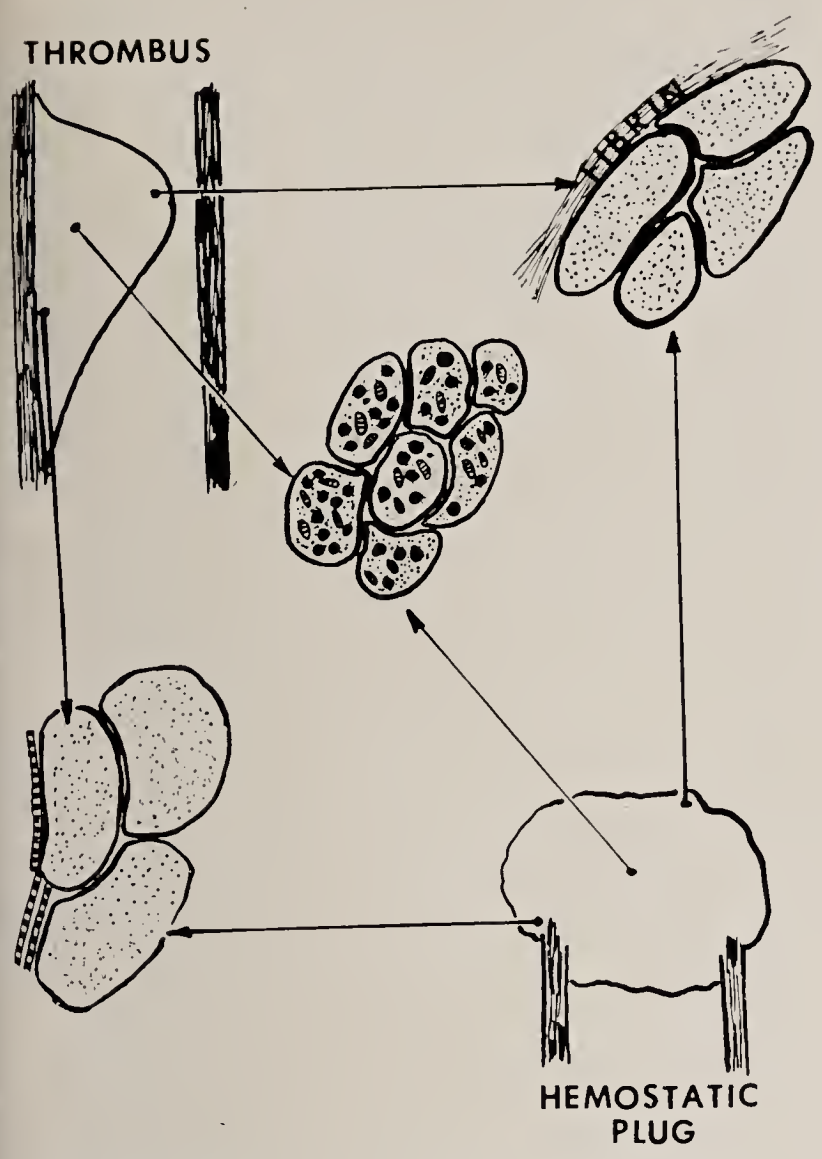


Figure 2: Structural similarities between a thrombus and a hemostatic plug.

ATP content of the red cells so greatly exceeds the ATP content of all the other formed elements of the blood, this observation can only be explained if red cells, as well as platelets, degrade ATP to ADP in response to stimuli provided by collagen fibrils and thrombin. If a small part of the ADP so formed were released into the plasma, a very powerful stimulus for platelet aggregation would result.

There is some indirect clinical evidence that the red cell may play a role in hemostasis and thrombosis. It has been recognized that thrombosis occurs much more frequently in patients with polycythemia than in the general population, while the bleeding times of anemic patients tend to be prolonged.[10] At present no acceptable hypothesis is available to explain these two observations. Research into the basis of these observations is hampered by the fact that there are other variables involved in the consideration of the red cell role: namely, the hematocrit and the blood viscosity, both of which are known to alter the coagulation mechanism.[11]

Thrombi tend to form in areas of disturbed blood flow such as at points of vessel bifurcation. Figure 3 presents a speculative picture of the effect of high velocity gradients present in areas of disturbed flow on the formed elements of the blood, such as the red cell. The large shearing forces acting across the cell surface may tear the cell membrane, thus releasing ADP, hemoglobin, phospholipids and enzymes into a small volume of plasma. A sufficient concentration of ADP may then result to initiate platelet aggregation. The release of phospholipids would promote thrombin production. Red cells have been shown[12] to contain a thromboplastic factor that activates the intrinsic pathway of coagulation via antihemophilic globulin (AHG, factor VIII). The release of this material would further enhance thrombin formation.

Research on response of red cells to circulatory trauma

With these factors in mind, the response of red cells to the trauma received during circulation was investigated and its relevance to the pathogenesis of thrombosis considered. As an index of red cell damage, the amount of hemoglobin liberated into the plasma during a period of *in vitro* circulation was measured. Variations in the rate of hemolysis with variations in the hematocrit were studied.

a) *Materials and Methods*

(i) Preparation of animal blood

Fresh porcine blood was obtained daily from Canada Packers Limited. After the animals were stunned with carbon dioxide, their throats were slit and blood from each animal individually collected in separate siliconized glass containers containing one part ethylenediamine tetra-acetic acid (EDTA) anticoagulant (2 g. EDTA and 0.33 g. sodium chloride per 100 ml. solution, pH 7.4) for every nine parts blood to be collected. The blood was centrifuged in 250 ml. containers in a Servall RC-3 refrigerated centrifuge for 10 minutes at 200 G and the platelet-rich plasma removed. The red cells were resuspended in Tyrode's Albumen buffer and washed by centrifugation at 500 G for 10 minutes. The supernatant, buffy coat and upper layer of red cells (which was contaminated with white cells) were discarded and the remaining red cells resuspended and rewashed as before. The remaining cells after the second washing were packed by centrifugation at 4000 G for

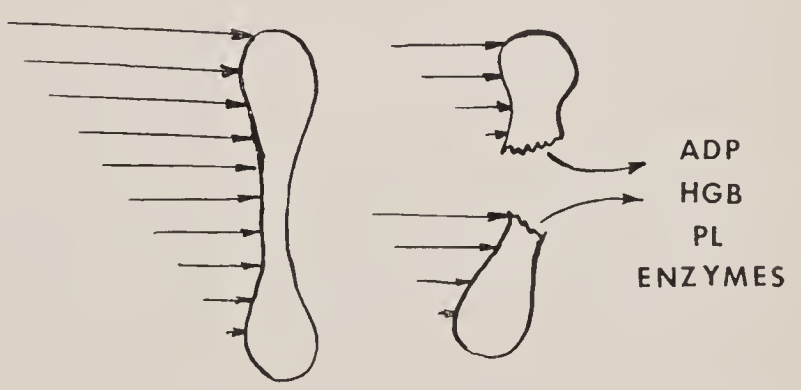


Figure 3: Proposed mechanism of hemolysis of bred cells in areas of turbulent flow. Arrows indicate magnitude of velocity gradient and release of red cell contents.

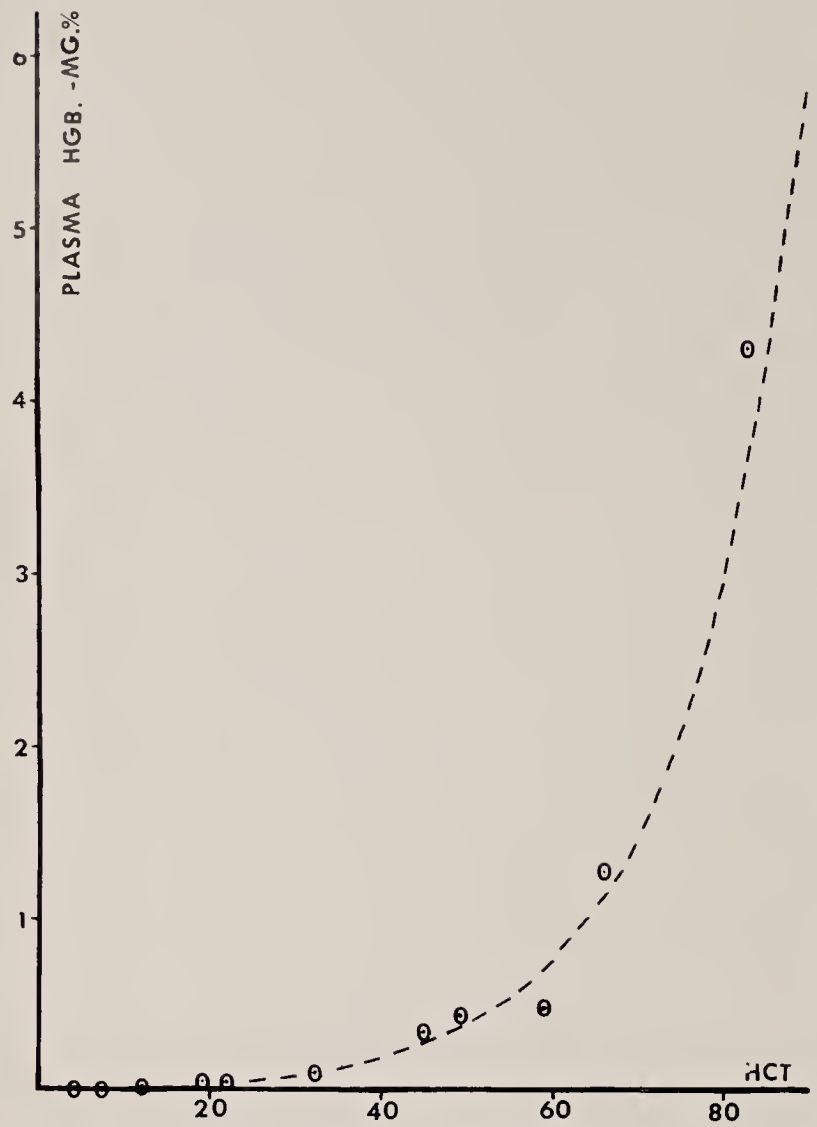


Figure 4: The free plasma hemoglobin (in mg. per cent) plotted against hematocrit. The relationship is expressed by:

$$\text{plasma hemoglobin (mg.\%)} = 0.0128.e^{0.691.Hct} \quad (p < 0.001)$$

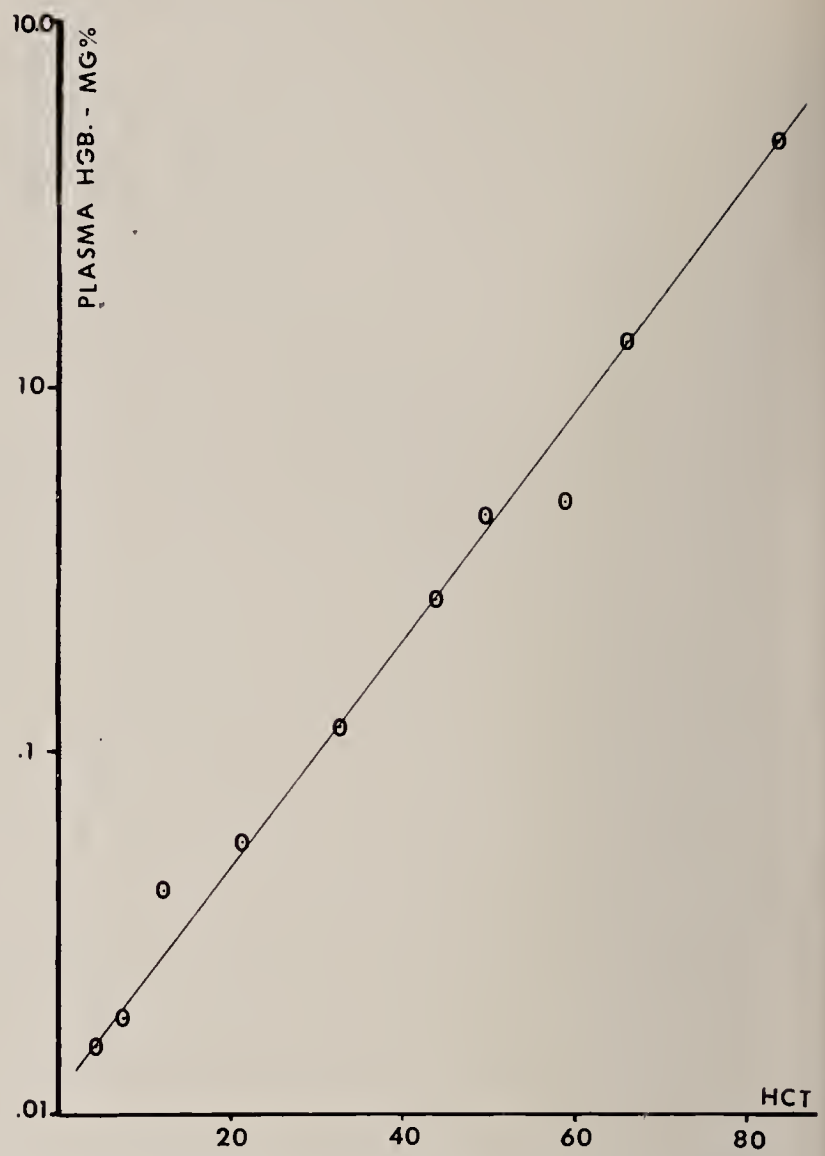


Figure 5: The plasma hemoglobin (in mg. per cent) plotted on a semilogarithmic scale against hematocrit. The relationship is expressed by:

$$\log_{10} \text{plasma hemoglobin (mg.\%)} = -1.89 + 0.03.Hct \quad (p < 0.001)$$

10 minutes. This preparation procedure did not cause any significant red cell hemolysis. Red cell suspensions were then prepared to have varying hematocrits, using Tyrode's Albumen buffer with added calcium and magnesium ions as the suspending medium.

(ii) Preparation of human blood

Fresh human blood was obtained from the Red Cross blood donor clinics within 2-4 hours of venesection. The standard acid-citrate-dextrose (ACD) anticoagulant was used. The red cells were packed without washing at 4000 G for 10 minutes. Red cell suspensions were prepared to have varying hematocrits using the plasma obtained during the backing procedure as the suspending medium.

The hematocrit (Hct) values of the suspensions were determined using a Clay-Adams microhematocrit apparatus. Values used are the mean of three determinations. The range of hematocrits investigated was 3.6% to 83.8%.

The red cell suspensions were placed in a 50 cm. length of siliconized polyvinyl chloride tubing (internal diameter 3/16") connected to a 30 cm. length of siliconized glass tubing (internal diameter 3/16"), both being joined to form a closed loop of approximately 12 ml. volume. A flow rate of 123 ml. per minute at a pulse rate of 200 per minute was employed, using a Harvard Apparatus peristaltic pump (Model 500-1200). The pump occlusion plate was set to maintain an end pressure of 500 mm. Hg. Under these conditions the pressure inside the loop during the period of circulation was approximately 100/75 mm. Hg. All samples were circulated for exactly ten minutes.

Control (uncirculated) and circulated samples were centrifuged at 4000 G for 2 minutes immediately after the ten minute circulation period and the supernatant removed for analysis of its free hemoglobin content. All free hemoglobin values reported are the difference between the circulated and the control samples.

Hemoglobin (Hgb) was measured by the method of Drabkin[13], the optical density of the cyanmethemoglobin derivative being measured at 540 millimicrons in a Zeiss spectrophotometer. The percentage hemolysis was calculated from the relation:

$$\% \text{ hemolysis} = \frac{A - B}{T - B} \times 100. \quad (1)$$

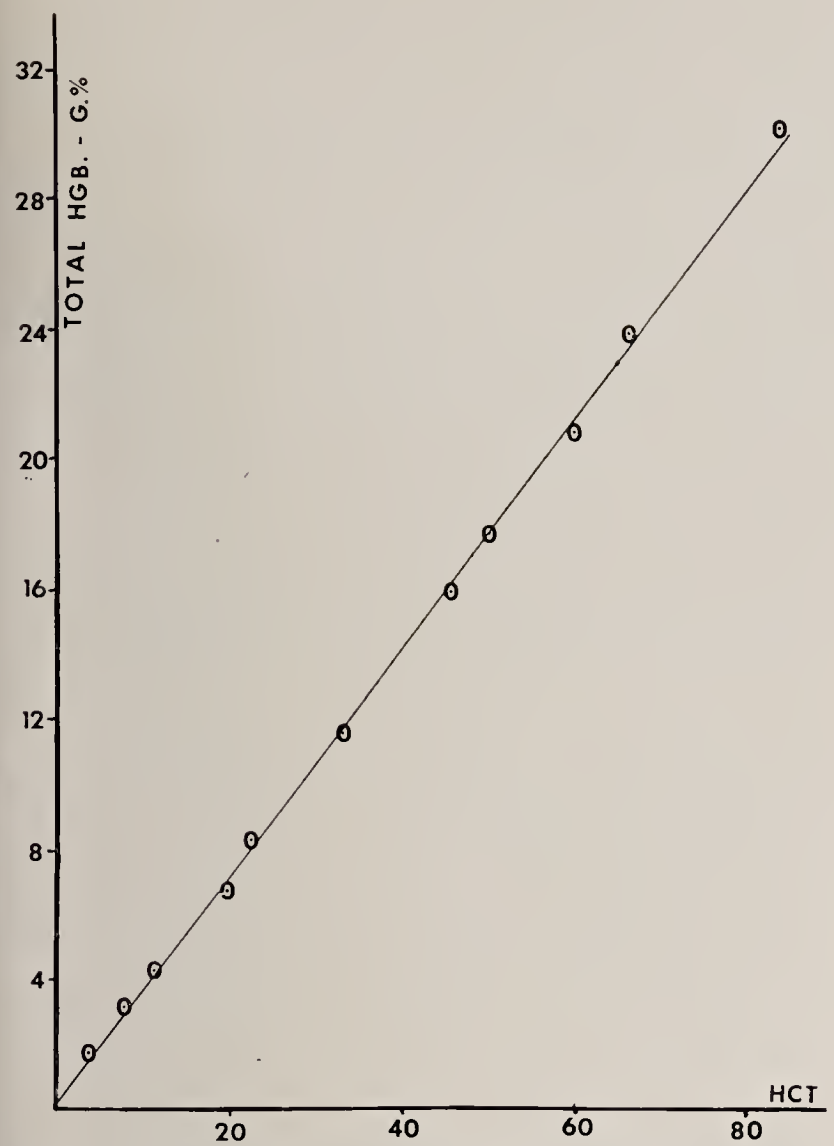


Figure 6: Total hemoglobin content (in grams per cent) of the red cell suspension plotted against hematocrit. The relationship is expressed by:
Total hemoglobin (g.%) = 0.00 + 0.35.Hct ($p < 0.001$)

where:

A = free hemoglobin after circulation (circulated sample)

B = free hemoglobin before circulation (control sample)

T = total hemoglobin in red cell suspension.

Linear regressions on the data obtained were performed on an IBM 7094 computer. The correctness of the fit of the data to the calculated line was estimated by means of a Student's test.

b) *Results*

The results are summarized in Figures 4 to 7. There was no essential difference in the nature of the response of human and porcine red cells, although absolute values obtained varied from day to day. The values reported are for porcine cells which were observed over the widest range of hematocrit values. Since there was no essential differences in the results using plasma and Tyrode's Albumen buffer as suspending medium, the free hemoglobin in the suspending medium will be referred to as plasma hemoglobin.

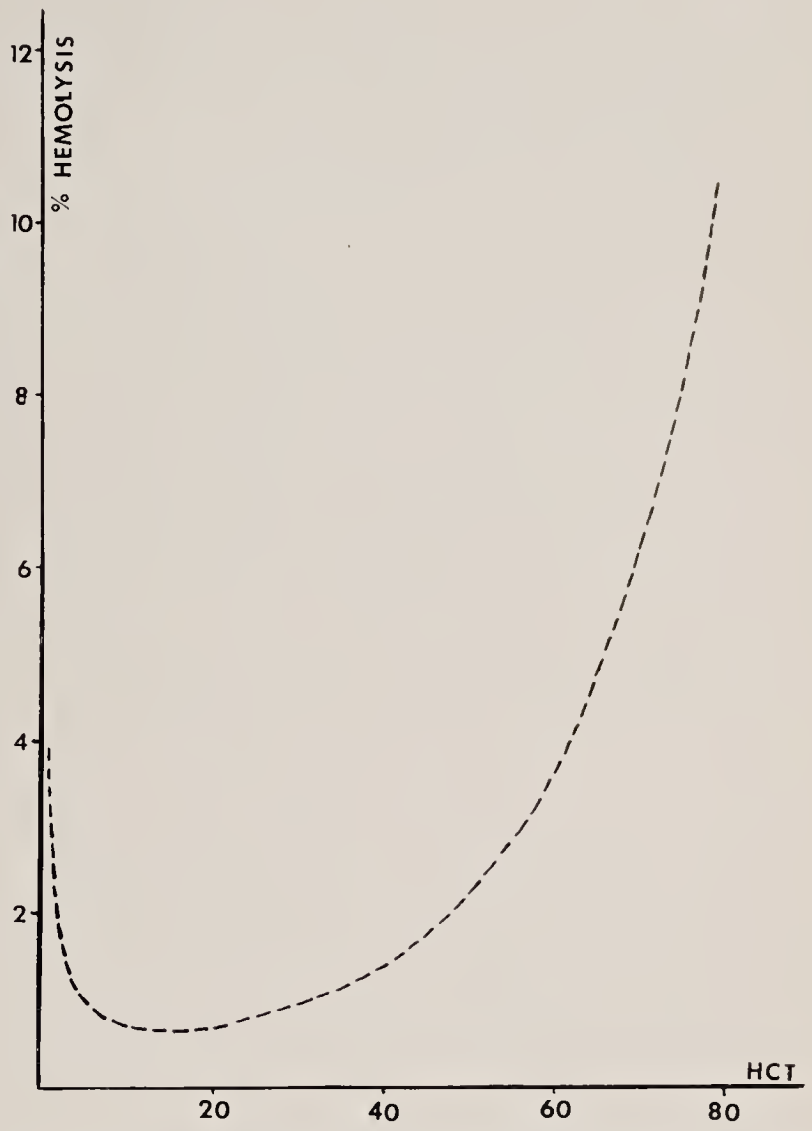


Figure 7: Calculated percentage hemolysis plotted against hematocrit. The relationship is represented by:

$$\% \text{ hemolysis} = \frac{3.68.e^{0.691.Hct}}{Hct} \qquad (p < 0.001)$$

The plasma hemoglobin, in mg. per cent, released during ten minutes of *in vitro* circulation varied exponentially with the hematocrit of the red cell suspension. (Figure 4) This relationship can be reduced to a linear function if the logarithm of the plasma hemoglobin is plotted against hematocrit. (Figure 5). The values obtained for these relations were:

$$\text{plasma hemoglobin (mg.\%)} = 0.0128.e^{0.691.Hct} \qquad (II)$$

and:

$$\log_{10} \text{plasma hemoglobin (mg.\%)} = -1.89 + 0.03.Hct \qquad (III)$$

where e is the base of natural logarithms and is approximately 2.71828.

Since the total hemoglobin content of a red cell suspension is a linear function of the hematocrit (Figure 6) and could in this experiment be represented by:

$$\text{Total hemoglobin (g.\%)} = 0.00 + 0.35.Hct \qquad (IV)$$

the percentage hemolysis can be calculated by substituting for the numerator of relation (I) a value from

relation (II) and for the denominator of relation (I) a value from relation (IV). The result obtained is:

$$\% \text{ hemolysis} = \frac{3.68.e^{0.691.Hct}}{Hct} \qquad (V)$$

This has the general form:

$$\% \text{ hemolysis} = \frac{k.e^{a.Hct}}{Hct} \qquad (VI)$$

where: k is a constant
a is the slope of the log plasma hemoglobin versus hematocrit curve (Figure 5).

This relationship represents a J-shaped curve, as shown in Figure 7.

All relationships were statistically significant ($p < 0.001$).

Discussion

The results obtained in this study are similar to those obtained by Shen, Castle and Fleming[14] and by Fok and Schubothe[15] who created local turbulence in blood samples by rotating flasks of blood containing glass or quartz beads. Their work did not cover as wide a range of hematocrit values as did the present study and so the nature of the lower end of the percentage hemolysis-hematocrit curve was not appreciated by them. They could not fit this curve to either a linear or a simple exponential relationship. The shape of the curve they obtained is the same as that in Figure 7 for the range of hematocrit values which they used.

If the free hemoglobin released in these experiments were to be taken as an index of red cell contents released into the plasma (including ADP, phospholipids, enzymes, etc.) the results of this study may help to explain certain recent clinical studies. Burch and DePasquale[10] reported that patients with myocardial infarction had significantly higher hematocrit values than did a group of control patients. Although this finding was disputed by Conley[16], it has been confirmed by Mayer[17] who performed the first adequately controlled study by measuring hematocrits under carefully standardized conditions. An examination of Figure 4 shows that as the hematocrit rises from 40% to 50%, the amount of hemoglobin released into the plasma doubles. If the amount of ADP, etc. were also to double, the plasma defence mechanisms might be overwhelmed and thrombosis result. Experiments to demonstrate whether or not this actually occurs in vivo have yet to be performed.

SUMMARY

The effect of the hematocrit value on the hemolysis of the red cell during blood flow was investigated *in vitro*. The percentage hemolysis observed could be related to the hematocrit and expressed by the following equation:

$$\% \text{ hemolysis} = \frac{k.e^{a.Hct}}{Hct} \qquad (VII)$$

where k and a are constants. The significance of this study is related to recent reports of an elevation of hematocrit values in patients with angina pectoris and myocardial infarction. The current concept of the mechanisms of hemostasis and thrombosis are reviewed and a role for the red cell in them suggested.

J. A. Wright 6T8

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The Primary Vasculitides

Michael Bach 6T7

The "secondary" vasculitides are usually considered as those where a definite etiological factor secondarily involves the blood vessels; thus, an acute bacterial infection with septic emboli, abscess formation in the region of a blood vessel, or mycotic or parasitic infection may all give rise to a vasculitis. The primary vasculitides, on the other hand, are those in which the vascular injury appears to be the primary pathology. Kussmaull and Maier, in 1866, were probably the first to document the strange clinical entity which later became known as Polyarteritis Nodosa (PAN), and it was only much later with the advent of skin and muscle biopsies that the pathology and course of this vasculitis was fully described. In 1952, Pearl Zeek outlined her now famous classification of what she called "the necrotizing angiitides".[2] The classification was almost entirely a pathological one with the disease differentiated on the basis of location and size of the vessel affected, and the type of inflammatory cell response found. (Table 1).

TABLE 1: ZEEK'S CLASSIFICATION

1. Idiopathic Polyarteritis Nodosa
2. Hypersensitivity Angiitis
3. Wegener's Granulomatosis
4. Allergic Granulomatous Angiitis
5. Giant Cell Arteritis
6. Rheumatic Arteritis
7. Secondary Polyarteritis
8. Miscellaneous

Rose and Spencer, in 1957, challenged Zeek's classification maintaining that on the basis of the clinical picture the vasculitides need only be differentiated into two distinct groups: those with and those without lung involvement.[3] Gardner felt a convenient classification was based simply on the size of vessel affected. Recently, Alargon-Segovia (Table 2) has devised a comprehensive classification in which he attempts to deal not only with the major vasculitides, but also with the lesser known syndromes which seem to fit well into his concept of angiitis versus granulomatosis. This article is an attempt to trace some of the past efforts and outline current trends in piecing together a workable and functional classification of the angiitides.

TABLE 2: ALARGON-SEGOVIA'S CLASSIFICATION

A. Specific Vasculitides
   1. Polyarteritis
   2. Hypersensitivity Angiitis
      a) Goodpasture's Syndrome
      b) Erythema Nodosum
      c) Erythema Multiforme
      d) Anaphylactoid Purpura
      e) Nodular Vasculitis
      f) Rheumatic Arteritis
   3. Allergic Granulomatous Angiitis
      a) Loeffler's Syndrome
   4. Wegener's Granulomatosis
      a) Lethal Midline Granuloma
   5. Giant Cell Arteritis
      a) Takayasu's Syndrome
   6. Thromboangiitis Obliterans

B. Vasculitis Associated with Collagen Disease
   1. Disseminated Lupus Erythematosis
   2. Scleroderma
   3. Rheumatoid Arthritis
   4. Dermatomyositis

Connective tissue and connective tissue of blood vessels in particular, can react to injury in only a limited number of ways.[1] Because of this fact, attempts to classify vasculitis and to define its etiology exclusively by its pathological picture have necessarily been doomed to failure. Most authors consider five definite pathological changes and appearances as characteristic of the response of connective tissue to injury:

1. MUCINOUS EDEMA

It has been noted in the collagen diseases and also in experimental models that an early sign has been the appearance of a mucinous substance separating the collagen fibres and being "deposited" in the walls of blood vessels. Histochemical analysis reveals this substance to be acid mucopolysaccharide.

2. FIBRINOID NECROSIS

This term was applied to an acidophilic homogeneous substance with the staining properties of fibrin appearing in the walls of the blood vessels. There has been no resolution of the argument as to whether this material is indeed fibrin deposition, collagenous degeneration, or, as is the case in some of the collagen diseases, gamma globulin deposition.

3. GRANULOMA FORMATION

This is one manifestation of chronic inflammation and is characterized by the persence of epithelioid cells and giant cells arranged in nodular formation surrounded by cuffs of mononuclear cells.

4. FIBROSIS

As a result of the inflammation and inflammatory cell infiltration and destruction, fibrosis occurs as a reparative phenomenon.

5. HYALINIZATION

Here a transformation of the cellular and tissue components into an extremely amorphous "clear" substance occurs.

Most of the current literature will attest to the fact that there is as yet no clear cut pattern to these various diseases. To aid in some undersanding of them, they will be discussed as individual syndromes rather than as a "hodge podge" of possibly related, possibly unrelated entities.

A. SPECIFIC VASCULITIDES

1. POLYARTERITIS

The classical pathological picture of this disease is one of segmental inflammation of the entire wall of a muscular artery. It usually begins with fragmentation and degeneration of the adventitial collagen. A fibroblastic and histiocytic proliferative response follows in focal areas of the advenitia. The next stage is characterized by the appearance of fibrinoid necrosis in the media and a pleomorphic inflammatory cell exudate, first polymorphonuclear leukocytes and later mononuclear cells. The entire vessel wall is involved in this process which, upon subsiding, heals by granulation tissue formation and sclerosis. The process is distinctive in that lesions are found in many muscular arteries in all stages of development. The clinical picture is easy to understand from the pathological course. Vascular accidents are possible in brain, myocardium, kidney, and intestines. Aneurysm formation, thrombosis, hemorrhage, and ischemic symptoms are all common features. In addition to this multisystem involvement, systemic signs of tissue necrosis such as weight loss, increased erythrocyte sedimentation rate, and fever are present. The disease occurs characteristically in older males and is definitively diagnosed by biopsy of skin or muscle. The interesting characteristic of this disease is that no vascular lesions are found in the lungs.

2. HYPERSENSITIVITY ANGIITIS

Usually the smaller vessels are involved; that is, arterioles, capillaries and even venules. The lesions have no predilection for bifurcations as PAN does, and are all found at the same stage of development. This stage corresponds to the fibrinoid necrosis and pleomorphic cellular exudate stage of PAN. In addition to the specific lesions in the pulmonary vascular tree that are characteristic of this disease, unusually severe necrotizing and exudative lesions are found in the glomeruli resulting in a necrotizing glomerulonephritis. There is usually no evidence of healing at autopsy. The clinical picture is characteristic. There is an abrupt onset of a diffuse pulmonary disease, renal involvement and other systemic manifestations following the administration of some therapeutic agent, usually sulfonamides. (Penicillin, Dilantin, and iodides have also been incriminated.) Often there is the development of severe asthma together with an eosinophilia.[4] The disease is usually rapidly fatal.

There are some other syndromes considered related to hypersensitivity angiitis on the basis of lung involvement and objective evidence of hypersensitivity.

a) *Goodpasture's Syndrome*

In adults, this disease usually presents with hemoptysis and severe anemia. Later there is evidence of a glomerulonephritis. The patient usually dies rapidly either from massive pulmonary hemorrhage, pulmonary edema, or terminal uremia. Arteritis, involving lungs, kidneys, and other organ vasculature has been noted frequently in this disease.[5] The etiology is totally unknown. A similar condition in children is called idiopathic pulmonary hemosiderosis.

b) *Erythema Nodosum*

This condition is commonly associated with sulfonamide administration, infection with streptococcus, tuberculosis or coccidioidomycosis, chronic intestinal disease (ulcerative colitis), and sarcoidosis. It is seen as raised inflamed nodules on the lower limbs. The pathological picture is a vasculitis of the subcutaneous tissue with an accompanying mononuclear cell infiltrate.[6]

c) *Erythema Multiforme*

In this syndrome, there is a characteristic dermatologic picture of widespread, varied maculo-papulo-vesiculo-bullous lesions. The lesions are to be considered a hypersensitivity response to a foreign antigen, either infectious (viral), or chemical (sulfa, penicillin). The pathology is an "allergic" vasculitis, with eosinophilic infiltration of the vessel wall with some fibrinoid necrosis.

d) *Anaphylactoid Purpura*

This is a systemic disorder usually seen in young children and thought to have some relation to a state of hypersensitivity developing to some infecting organism. (A recent history of a mild infection can usually be elicited.) It is seen as a maculopapular sometimes hemorrhagic rash suddenly appearing on the lower extremities of a child who may concurrently complain either of abdominal or joint pain. These pains are evanescent and the condition usually clears in four to six weeks. Occasionally there is renal involvement and this can progress to a chronic nephritis. The pathological changes are again a vasculitis with secondary involvement of various viscera.

e) *Nodular Vasculitis*

A strange condition very similar to erythema nodosum, this disease presents with localized recurrent deep nodules in the connective tissue of legs of "healthy" people. The vessels involved are usually small

arteries and veins and the lesions progress to thrombosis and eventual fibrosis.

f) *Rheumatic Arteritis*

The relationship between previous infection with the streptococcal antigen and development of the vascular lesions is currently being clarified. Here the essential vascular change is a fibroblastic thickening of the walls of blood vessels with evidence of fibrinoid necrosis only being found in the Aschoff bodies and subcutaneous nodules.[13] The lesions affect medium as well as small sized vessels and have very little inflammatory cell infiltrate. The clinical manifestations of these lesions are seen as carditis and an arthritis.

3. ALLERGIC GRANULOMATOUS ANGIITIS

Churg and Strauss coined this term to denote a disease characterized by the development of granuloma in vascular and extravascular areas, and the presence of an "allergic" disease.[7] Clinically, the patient with a long history of asthma develops a high fever, eosinophilia, and symptoms of a diffuse terminal illness. The pathological condition differs from hypersensitivity angiitis in that large granulomata, sometimes even large enough to be palpable, are found in extravascular areas. Microscopically giant cells are characteristically arranged around the blood vessels which are involved with fibrinoid necrosis and the typical cell infiltrate. The extravascular granulomas have a core of eosinophils surrounded by histiocytes and giant cells.

a) *Loeffler's Syndrome*

Many consider this syndrome to be a benign localized form of allergic granulomatous angiitis, possibly because of its freedom from vascular involvement. In "severe" cases, however, areas of necrotizing vasculitis similar to PAN have been found. It classically consists of a pulmonary infiltrate, many eosinophils in the bronchial secretions, and a blood eosinophilia. It had usually been thought of in association with parasitic infestations, although in recent years it has appeared with no evidence of parasitic infestation.

4. *Wegener's Granulomatosis*

First documented by Wegener in 1936, this unusual disorder is characterized by the appearance of necrotizing granulomata of the ear, nose, sinuses, palate, pharynx, or larynx; that is, the upper respiratory tract. These are associated with a diffuse angiitis and a necrotizing glomerulitis.[8] The disease seems to pass through two stages. The first is a development of an ulcerating respiratory tract lesion with subsequent progression to a diffuse systemic angiitis and death usually from renal failure. The pathologic lesion involves the medium and small arteries and some veins. The diagnosis is made by biopsy of the respiratory tract lesion. The course to date is inexorable and steroids have no great effect.

a) *Lethal Midline Granuloma*

This is a localized progressive ulceration of the face leading to death in a few months with complete lack of response to antibiotics, steroids or even surgical débridement. There is no dissemination of the lesion and it must be differentiated from fungal and bacterial infections and from neoplasms (reticulum cell sarcoma).[9] It has been considered by many investigators as a localized "more benign" form of Wegener's in that although the granuloma does characteristically resemble Wegener's in size and structure, there is no systemic involvement. Characteristically, the patient feels otherwise well, and the only pathology worthy of note is a vasculitis in the granuloma itself.

5. GIANT CELL ARTERITIS

This disease characteristically affects an older age group. The usual presenting clinical features are headache and systemic upset. The commonly affected temporal arteries are tender and thickened and sometimes palpable; visual disturbances are a possible complication of internal carotid involvement. The disease follows a benign course and usually clears spontaneously within one to two years. The pathological picture includes inflammatory cell infiltration of all three coats of medium sized arteries with muscle degeneration and possible thrombosis. Giant cells are common.

a) *Takayasu's Synydrome*

Takayasu, a Japanese ophthalmologist, described a condition occuring in young females presenting with wasting of the upper half of the body, claudication of the arms, vertigo upon rising, and other signs of cerebral and upper limb ischemia.[11] The lesion here is an aortitis affecting specifically the exit points of the major vessels to the head and neck. The course of this disease is progressive and usually fatal. The microscopic pathology is similar to that of giant cell arteritis, but it is considered a different entity because of the different distribution of the lesions, sexes affected, and prognosis.

6. THROMBOANGIITIS OBLITERANS

Commonly known as Buerger's disease, this entity is included here for completeness. The question of whether this disease truly exists has been bandied around for years. McKusick has written a very impressive paper arguing for its existence.[12] The entity described is one which occurs in young adult males who are heavy smokers. They develop, after a few bouts of flitting superficial thrombophlebitis, evidence of vascular insufficiency of the upper and lower limbs. There is no evidence of diabetes, hypercholesterolemia, or heart disease (embolic phenomena), and the progression is prevented by cessation of smoking. Arteriography usually reveals evidence of scattered peripheral segmental lesions. Pathologically, acute lesions demonstrate microabscesses in a recent thrombus, with giant cells, polymorphonuclear leukocytes, and epithelioid

cells. There is some chronic inflammatory cell infiltrate in the wall of the vessels, but not usually any evidence of actual necrosis. It has not yet been decided whether this disease starts in the blood i.e. involving primarily the thrombus, or in the wall of the vessel.

B. VASCULITIDES ASSOCIATED WITH COLLAGEN DISEASE

The other large subdivision of vasculitis is that associated with the collagen disorders. The principle pathological feature varies with the disorder, but usually one of the five responses to connective tissue injury predominates.

1. DISSEMINATED LUPUS ERYTHEMATOSIS (DLE)

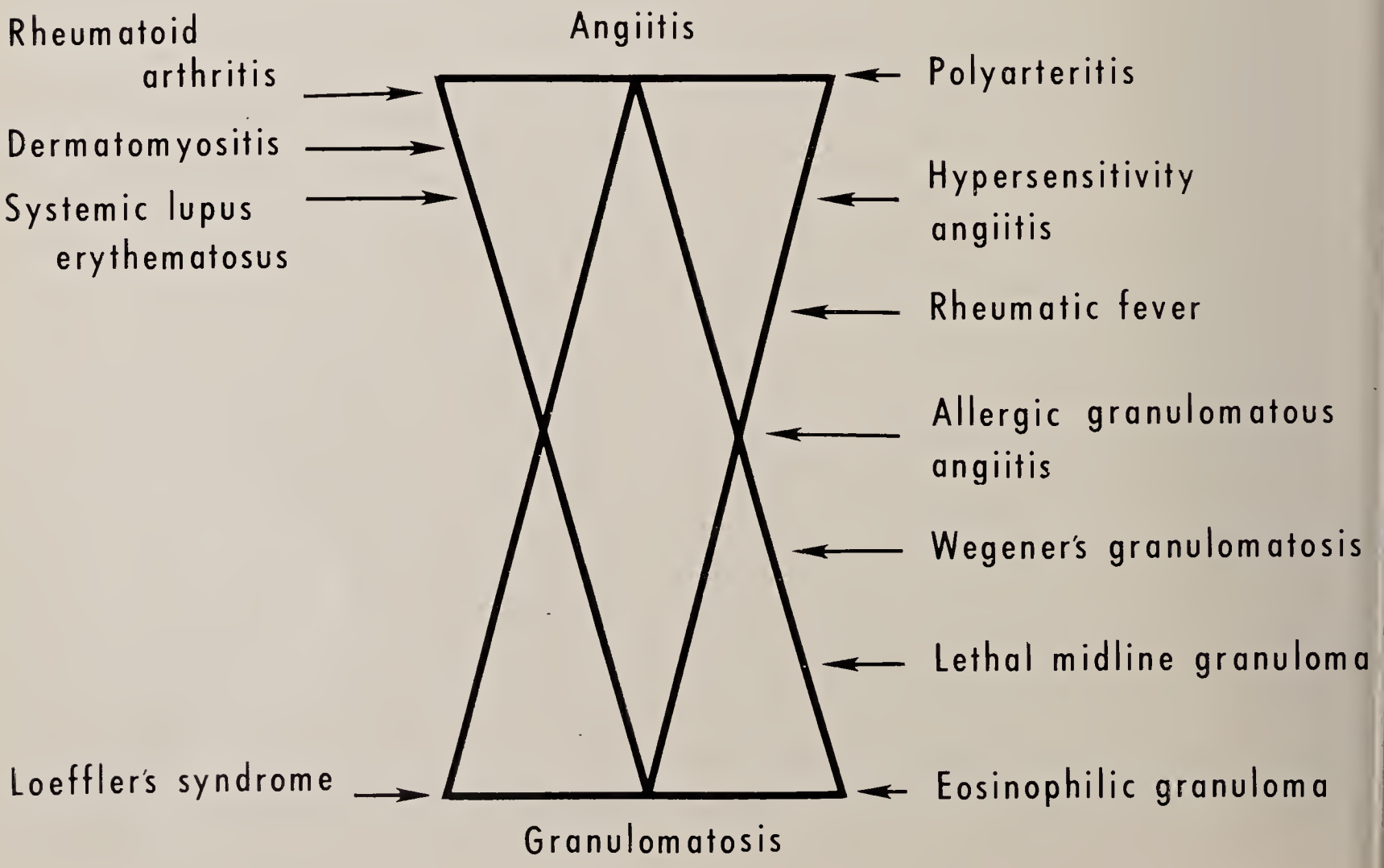
There is typically a generalized disturbance of connective tissue, but the system derangements are probably secondary to a vasculopathy in most instances. The vasculitis found, however, is not pathognomonic of this disease. The essential characteristic of the vessel pathology is a marked fibrinoid type of deposition in the initima of small vessels. There is little inflammatory response or fibroblastic proliferation, although some cases demonstrate vascular lesions identical to those of PAN. The clinical manifestations of this disease are well known by their heterogeneity. Polyserositis, arthropathy, glomerulonephritis, and pneumonitis, form only a part of the wide spectrum of disordered function.

2. SCLERODERMA

Progressive systemic sclerosis of the medium and small vessels of the body characterizes this disorder. Mucoid degeneration is found frequently in the walls, and occasionally vascular lesions similar to PAN are also found. This disorder is a generalized sclerosis of collagenous tissue. Its characteristic skin lesions are not a result of its vasculopathy, while the pulmonary alveolo-capillary block, the renal glomerulosclerosis and hyalinization, and the myocardial degeneration are considered to be secondary to the vascular sclerosis. In addition, the renal lesions exhibit areas of fibrinoid necrosis which cannot be differentiated microscopically from the lesions of malignant hypertension.

3. RHEUMATOID ARTHRITIS

The pathological features of this disease are well known. The arteritis, in this case, involves the walls of small arterioles in scattered areas and presents the characteristics of PAN at some times and a non-necrotizing segmental arteritis of striated muscle at other times. This arteritis has been proposed by some as the basic lesion in this disease. It has been well recognized that gangrene of the extremities and peripheral neuritis are complications of this disease and arteritis has been implicated in both. Severe onset of a PAN-like syndrome has been noted following the use of long term steroid therapy. The classical subcutaneous nodules are considered to have an underlying arteritis as their



initiator, with the characteristic picture of central fibrinoid necrosis surrounded by palisading of mononuclear cells, being extremely apparent.

Where are we left after considering this seemingly heterogeneous group of diseases all exhibiting a similar pathological picture? Certainly it is evident that one cannot relate them purely on the grounds of morphological similarity. From experimental studies by Rich and co-workers, it seems fairly clear that hypersensitivity plays an important role in diseases like hypersensitivity angiitis.[14] Serum injections into animals resulted in morphologically and geographically similar lesions, and fluorescent antibody studies identified gamma globulin in the involved arteries. Hypertension as the cause of PAN has been postulated by many workers. Selye, in Montreal, produced histologically similar lesions in vessels of dogs who had received infusions of DOCA.[15]

It is obvious that the preceding classifications of the vasculitides leave much to be desired. What appear to be definite clinical syndromes are merely shades in a whole spectrum of disease entities which merge one with another. Fienberg tried to capture this idea when he penned the term "Pathergic Granulomatosis" as implying the evidence of granulomatous disease encompassing all states in which there was an alteration of tissue reactivity.[16] He considered this entity to be divided into two main classes; disseminated pathergic granulomatosis and focal pathergic granulomatosis. Alargon-Segovia also considers the necrotizing vasculitides to be part of a wide spectrum ranging from pure granulomatous changes to pure angiitis (diagram).[17] Whether the various collagen diseases are all part of the same process with just different pathological changes being emphasized has still to be decided.

To say the least, the field of the vasculitides remains confusing and bewildering. Clinical pictures sometimes are made up of characteristics from supposedly different diseases, and the suggested classification then fails. No classification will probably be workable until some understanding of the underlying etiological and pathogenetic process is achieved.

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Tumors And Malformations Of Blood And Lymph Vessels

M. B. Buckspan, D.D.S. 6T7

Although, discussion of vascular and lymphatic abnormalites and malformations is complicated by the lack of agreement on the nature of many of these lesions, an angioma might fit into at least one of four distinct etiological categories, Congenital Malformation, Acquired Angiectasia, Granuloma Formation, Neoplasia.

TABLE 1
CLASSIFICATION OF VASCULAR MALFORMATIONS AND TUMOURS

I Vascular Hamartoma	a) Hemangioma	i) Capillary ii) Cavernous
	b) Lymphangioma	i) Capillary ii) Cavernous
II Telangiectasia	a) Simple b) Spider c) Hereditary hemorrhagic	
III Granuloma	a) Granuloma Pyogenicum b) Epulis	
IV True Angioblastic Neoplasms	a) Glomangioma b) Hemangiopericytoma c) Hemangioendothelioma d) Hemangioendotheliosarcoma e) Lymphangiosarcoma f) Kaposi's Sarcoma	

I Congenital Malformation (Vascular Hamartoma)

This concept[1] was introduced to describe tumor-like, non-neoplastic malformations, characterized by abnormal mixtures of normal tissues indigenous to that part. Most of these tumors are present at birth, although not necessarily evident at that time. There are no features of the tissue architecture that distinguish true angiomas from vascular hamartomas, both consisting of tangles of supernumerary vessels. The growth of the hamartoma is not progressive, but is maintained within the boundaries of the parent tissue. The enlargement that may occur is usually the result of hemorrhage or inflammation within the mass rather than of cellular proliferation.[2]

II Acquired Angiectasia (Telangiectasia)

The great majority of these lesions are acquired. Telangectasia means dilatation of the terminal vessels. They are important because an association often exists between telangiectases and related disease in other tissues.

III Granuloma Formation

Some vascular masses are acquired and represent a reparative process. These are in fact post-traumatic or post-inflammatory and occur as a result of excessive or thwarted healing.

IV Neoplasia

Neoplasms of vascular origin are uncommon. However, it is important that true neoplastic tumors be recognized, and not confused with other vascular lesions. Vascular hamartomas are not well demarcated, and give false impressions of invasion. Further confusion may arise when finding multi-centric formation of these lesions, resembling metastatic foci. Metaplasia in benign proliferations of mesenchymal tissue as well as a high degree of vascularity in certain tumors also lead to misinterpretation and false labelling of other tumors as angiomas.

I Vascular Hamartoma

a) *Hemangioma*

i) Capillary Hemangioma

Capillary hemangiomas are composed of vessels that are of the caliber of normal capillaries. They usually appear in skin, subcutaneous tissue, and mucous membrane, but may be found in visceral organs. Grossly, they are red to blue in color, may be pedunculated or flat, and cover large areas of skin. Microscopically they are non-encapsulated, but circumscribed, and consist of capillary-sized vessels, with projections into the surrounding tissue. These projections do not represent malignant invasion but growth along tissue planes.

ii) Cavernous Hemangioma

These occur in skin and mucosal surfaces and occasionally in viscera. The distinguishing feature is formation of large cavernous vascular channels. Clinically they are red, soft masses, frequently raised above the skin. Reactions such as fibrosis, thrombosis, or rupture of vascular channels may take place within these lesions and thereby modify their appearance. Progressive fibrosis, over many years within a capillary hemangioma probably accounts for the formation of a sclerosing

hemangioma. There is much disagreement as to whether this lesion is in fact of vascular origin. Progressive sclerosis transforms these tumors into a predominantly cellular mass, the vascular channels having been obliterated. Microscopically, whorls of spindle-shaped cells, partially obliterated vessels, lipid, and pigment can be seen.

Malignant transformation within hemangiomas is extremely rare. Occasionally a peculiar formation of degenerated, calcified vessels may be found within these tumors. Hemangiomas are found in most tissues of the body, and may be multiple in different sites, or associated with other defects giving rise to the multiple hemangiomatous syndromes. The following are a few representative examples of these syndromes. *Sturge-Weber syndrome*[3] consists of cutaneous angiomatosis usually within the distribution of the trigeminal nerve, with associated meningial angiomas. The coexistence of angiomas co-existing with enchondromas or dyschondroplasia of bones is called *Maffucci's syndrome*.[4] Any combination of retinal angiomas and angiomas of the brain, especially cerebellum, with cysts of pancreas or kidney or renal cell carcinoma form a syndrome-complex known as *von Hippel-Lindau disease*. In children a condition occurs in which thrombocytopenia is associated with giant hemangiomas.[5] It is thought that the phatelets are actually destroyed within the hemangioma. *Klippel-Trenaunay syndrome*[6] is a unilateral condition in which a limb affected with hemangioma undergoes hypertrophy. In premature infants retrolental fibroplasia may be associated with cutaneous hemangiomas.

b) *Lymphangioma*

Lmyphangiomas are malformations arising from lymphatic channels, and as such, are analagous to hemangiomas.

i) Capillary Lymphangioma

They are small, raised masses composed of lymph vessels. Occasionally, elements of both blood and lymph channels are found in the same lesion. These benign innocuous lesions are treated by excision.

ii) Cavernous Lymphangioma

These benign lesions are usually found in the neck, axilla, arm and occasionally retroperitoneally. In the neck they are known as cystic hygromas. They consist of large cystic spaces lined by cells which secrete a lymph-like fluid. Associated with these spaces are smooth muscle cells, irregular blood vessels and lymphoid tissue. Treatment by excision is difficult because of the projection into contiguous tissue.

II Telangiectasia

These are not true tumors but are abnormal vasodilatations of arterioles, venules, or capillaries in skin or mucous membrane.[7] Clinically, they are small red lesions and represent either acquired exaggerations of pre-existing vessels or congenital malformations.

a) *Simple Telangiectasis*

This lesion results from chronic exposure to physical agents such as sun, wind, or heat, or may be secondary to chronic venous insufficiency. Histologically it consists of dilated capillaries. Obliterative treatment by electrocautery or selerosing injections is usually instituted for cosmetic reasons.

b) *Spider Telangiectasis*

Spider Telangiectases are either congenital or acquired. The former is not significant, while the latter is most often associated with liver disease usually cirrhosis, and with pregnancy. It has been suggested, but never confirmed that the underlying factor in both conditions is hyperestrogenism. They are most often found on the face, neck, upper arms and chest and rarely appear on the lower half of the body. The typical lesion is a focal subcutaneous network of vessels radiating from a central arteriole which if compressed, results in blanching of its vascular network.

c) *Hereditary Hemorrhagic Telangiectasia*
(Rendu-Osler-Weber Disease)

This is a clinical entity, characterized by multiple small punctate telangiectases of skin and mucous membrane present from birth and recurring hemorrhage. It is inherited as a Mendelian dominant trait affecting both sexes. Patients with this disease usually present with recurrent hemorrhages from the mucous membranes.

Another interesting disease is Ataxia-Telangiectasia. This is characterized by oculocutaneous telangiectases, progressive cerebellar ataxia, choreoathetosis, mental deterioration, and recurrent infections. This is a familial disease and usually becomes evident in childhood.

III Granuloma

a) *Granuloma Pyogenicum*

This lesion is known to the layman as proud flesh. It is a small pedunculated nodule of exuberant granulated tissue. Because of its ability to recur after removal and to grow extremely rapidly, as well as the microscopic finding of numerous, newly formed capillaries and wild endothelial proliferation, some authors consider it a true vascular neoplasm.[8] These lesions are particularly prevalent in and about the oral cavity. One example is the so called gingival pregnancy tumor. Glickman[9] regards this lesion as an angio-granuloma, similar in etiology to the granuloma pyogenicum formed as an exaggerated chronic inflammatory reponse to local irritation. The cause of the extreme sensitivity of the gingiva to irritation during pregnancy is not known but hormonal factors are, of course, postulated.

b) *Epulis*

An epulis is another inflammatory tumor-like lesion found on the gingiva. The general opinion is that these cell lesions are in response to local injury and not true tumors.[10] Their histologic appearance and gross tendency to extend into underlying alveolar bone give the false impression of neoplasia with invasion. These must be differentiated from the central giant-cell tumors of the jaw which are invasive and may metastasize.

IV True Angioblastic Neoplasms

Tumors arising from blood or lymph vessel endothelium and related structures such as the pericytes of Zimmerman are quite rare. These lesions range from benign to highly malignant species. Many individual lesions show gradations in cellular activity so that accurate classification is difficult. Division into benign and maliginant categories depends on two anatomic characteristics. They are the degree to which the neoplasm is composed of well-formed vascular channels, and the regularity of the endothelial cell proliferation.

a) *Glomangioma*

Anatomically the normal glomus is a convoluted arterio-venous anastomosis. The walls of these vessels contain cuboid epithelial-like cells which may be identical with the pericytes of Zimmerman, and are functionally akin to the smooth muscle cells of arterioles. Glomi are usually found in the skin but have been reported in other tissues. These tumors are usually small and single, and made up of vascular spaces with layers and masses of polyhedral glomus cells. Clinically, the majority of these tumors present as a single, small, superficially placed asymptomatic mass. The classical history of severe paroxysmal throbbing pain at night, associated with a subungual red mass is diagnostic, but is obtained infrequently. The treatment of choice for these benign tumours is local excision.

b) *Hemangiopericytoma*

An hemangiopericytoma is a tumor related to the glomangioma, but is less highly organized. Histologically it consists of masses of spindle-shaped cells, probably derived from pericytes, which lie packed between the vascular channels. Both sexes are affected equally, and the greatest incidence occurs in the fourth decade. A series from The Memorial Hospital in New York[11] revealed that most of the tumors presented as painless, slow-growing lumps, and are more highly malignant than previously thought. At the time of diagnosis, over half had metastasized by way of the blood or lymph to the lung. Treatment must be radical because local excision resulted in recurrence. These tumors were radio-resistant and not reponsive to chemotherapeutic agents.

c) *Hemangioendothelioma*

An hemangioendothelioma is a benign tumor of endothelial origin. Clinically these tumors are found most often in the skin, but may affect the viscera as well. They appear as reddish-grey firm masses and consist of sheets of endothelial cells, usually well ordered, and with little evidence of atypism. It is the increased cellularity that distinguishes these from hemangiomas. These lesions are benign and cured by local excision, but tissue analysis is mandatory.

d) *Hemangioendotheliosarcoma*

This tumor may be a malignant variation of an hemangioendothelioma or may be a separate and distinct entity.[12] Histologically, all degrees of differentation may be noted, even in the same tumor. The margins are ill-defined, and invasion is evident. The more anaplastic forms show markedly atypical pleomorphic cells which resemble endothelial cells lining vascular spaces as well as masses of spindle cells typical of sarcoma. Clinically this tumor metastasizes by the blood stream and also invades locally. Radical excision is the treatment of choice.

e) *Lymphangiosarcoma*

These are tumors characterized by endothelial cell proliferation and vascular channels resembling lymph capillaries, arising in limbs subject to post mastectomy lymphedema.[13] These tumors are found in different tissues, and may arise either de novo or rarely from malignant changes within a lymphangioma.

f) *Kaposi's Sarcoma*
(multiple idiopathic hemorrhagic sarcoma)

The nature of this lesion is very obscure. It appears as a proliferation of cells of the reticuloendothelial system, which may develop as spindle or giant cells resembling a lymphoblastoma.[14] They may be considered as a form of angiomatosis because of later evidence of increased cellularity and endothelial budding with resulting formation of vascular channels. If this activity is allowed to continue, the lesions undergo malignant change as evidenced by invasion, thus substantiating that this is indeed an angioblastic tumor. Most of the lesions appear in skin especially of the legs, but lymph nodes and viscera can be involved. These lesions are probably multicentric, primary foci, but the possibility of new lesions resulting from metastasis cannot be excluded. Progression of the disease is evidenced by lymphedema, ulceration of the extremities and occasionally involution of the nodule. There is considerable variation in the histology, with early lesions resembling granulomas, with budding vascular channels and endothelial proliferation. Later on infiltration of chronic inflammatory cells, hemosiderin deposition with extravasation of erythrocytes and increasing conective tissue proliferation, give these lesions a

definite sarcomatous appearance which correlates with the clinical features of invasion and metastasis. Radiotherapy is the treatment of choice, but this does not prevent development of new lesions.

SUMMARY

The nature, and certain characteristic of lymph and blood vessel tumors has been discussed. As pointed out, many of these tumors do not represent true neoplasms but are vascular malformations of congenital origin. These tumors form a heterogeneous group, and differ in their biologic characteristics as well as their physical appearance.

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Rudolf Virchow (1821-1902)
The Father of Modern Pathology

"He would conduct an examination from 8 to 10, would superintend a microscopic class from 10 to 12, would lecture from 12 to 1, would be in the Reichstag from 2 to 5, in the Town Council from 5 to 6, in some committee meeting of the Prussian Parliament from 6 to 7, and preside at the meeting of the Berlin Medical Society, or at the Anthropological Society, or deliver some popular address, or again do committee work from 7 to 9." [1]

The involvement of one man in such diversified fields is impractical in our time of narrow specialization. Even in his own era of the 19th century Rudolf Ludwig Karl Virchow was considered master of an eccentric vocational mixture.

Virchow was born in 1821 in a small town in Pomerania. He attended a local public school until 13 years of age and then spent four years at the gymnasium of Cöslin, in the chief town of the district. During these early years Virchow developed his facility for languages and attained a remarkable knowledge of Latin and Hebrew. He also learned Italian without a tutor in the few months available between finishing at the gymnasium and commencing the study of medicine at the Friedrick Wilhelm Institute. At this school, which educated medical officers for the Prussian army, he added lectures in logic, psychology, history, and Arabic poetry to his medical curriculum. Virchow escaped military service and after earning his degree in 1843 became Assistant to the Prosector of Anatomy at the Charité Hospital. Two years later he was chosen to head the department. In 1846 Virchow and Reinhardt founded the famous journal, *Archiv,* for which Virchow wrote and edited papers for the duration of his life.

In 1848 Virchow was sent to study the medical aspects of an epidemic of typhus fever in Upper Silesia; however, his report also dealt with the economic and social reforms necessary to prevent such outbreaks. His sudden political prominence as a result of this report coupled with his interest in social reform led to his election to the National Assembly in 1848. In this legislative body he advocated the establishment of a Ministry of Health and free medical education.

The study of pathology was not neglected during his early political career.

"Of his pathological work, the earliest was upon vascular disorders. He was the first to elucidate the true nature of phlebitis, thrombosis, and embolism, to recognize the essential features of leukaemia and to distinguish this condition from pyaemia, so laying the foundation for the brilliant work of Erlich and others upon haematology." [2]

Virchow proposed a novel theory of the hereditary nature of disease using three kings of Prussia, Frederick William the Second, Third, and Fourth, as his example.

"I know a family—a very exalted one—in which the grandfather had softening of the brain, the son hardening of the brain, and the grandson no brains at all." [1]

Virchow's political activity conflicted with that of the establishment, and he was forced to resign from the Charité. His reputation was already great, and he was offered a position by the University of Würzburg where he stayed from 1849 to 1856. There he researched on tuberculosis, cretinism, typhoid fever, congenital hydronephrosis, and amyloid degeneration of the liver to list only a few topics. In 1856 he left Würzburg to become Professor of Pathology at the University of Berlin where he remained for the duration of his career.

Virchow molded his research about two principles: first, a disease process must have an objective anatomical basis; second, conclusions concerning the nature of disease must adhere to the laws of cause and sequence.

> "Recognizing the value of Schwann's theory as showing that all physiological activity must be referred ultimately to the cell, that the cell is the seat of life, and that vital manifestations are due to its activity, Virchow showed that the same principle was equally valid for pathological relationships, and that in an abnormal modification of these same cellular activities is to be found the explanation of disease." [1]

Virchow delivered twenty lectures in 1858 which were published in a book, *Cellular Pathology, as based upon physiological and pathological histology*. This work is generally recognized as the foundation of modern pathology. In the preface he indicated a problem which has taken on even greater significance today.

> "Day to day do those who are obliged to consume their best energies in the frequently so toilsome and so exhausting routine of practice find it becoming less and less possible for them, not only to closely examine, but even to understand the more recent medical works." [3]

As a teacher Vichow was dynamic, and

> ". . . as he set the highest standard for himself, so he expected it in others. . . . He was at times perhaps unnecessarily severe and direct in criticism and students have told me that in examinations he treated them brutally. He had, at any rate, the reputation of being the hardest examiner 'to get by'." [4]

Virchow never shrank from controversy and firmly defended his ideas against Henle, Rokitansky, Hughes, Bennet, and Hueppe. He attempted to discuss his theories academically and to avoid personal feuds.

> "No doubt science cannot admit of compromises, and can only bring out the complete truth. Hence there must be controversy, and the strife may be, and sometimes must be, sharp. But must it even then be personal? Does it help science to attack the man as well as the statement? On the contrary, has not science the noble privilege of carrying on its controversies without personal quarrels?" [5]

He carried this philosophy into politics as the leader of the Radical Party in the Prussian Chamber from the time of his election in 1862 until his retirement in 1878. In 1865 Virchow defeated a Government motion to create a Germany navy and was subsequently challenged to a duel by Bismark. The offer was sensibly refused.

Virchow remained fully active throughout his life and immersed himself in many interests. He was an acknowledged leader in anthropological, ethnological, and archeological research and was President of the Germany Geographical Society for a number of years.

In January 1902, Virchow, 81 years old, fractured his femur in a fall from an electric tramcar. His health gradually declined over the months, and he died on September 5, 1902.

> "I uphold my own rights, and therefore I also recognize the rights of others. This is the principle I act upon in life, in politics, and in science. We owe it to ourselves to defend our rights, for it is the only guarantee for our individual development, and for our influence upon the community." [3]

B. N. French, B.Sc. 6T8

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PHOTOGRAPHS — *Courtesy Toronto Western Hospital*

I CLINICAL HISTORY

First Admission—October, 1961

This 28 year old man entered hospital on October 24, 1961 because of extreme shortness of breath and chest pain for about a week.

Past history revealed that the patient had been quite well until September, 1960, when he developed an intractable cough and symptoms of asthma. He discontinued smoking, with no improvement, although he had been smoking a pack a day. In August, 1960, he developed episodes of wheezing and lacrimation, for which he was given a bronchodilator. This helped him very little and a month later he was placed on Prednisone, which cleared his symptoms, so that he was asymptomatic by October, 1960. In November, 1960, all symptoms which he had experienced previously returned, associated with exertional dyspnea and sputum. Skin tests indicated sensitization to hair and house dust. A chest X-ray was normal. Injections to de-sensitize him were not successful, and discontinued in May, 1961. He was given steroids, 75 mg. of cortisone daily, and thereafter used them whenever the symptoms became severe. He did not return to see his doctor as requested. In September, 1961, the cough and dyspnea became worse, and he began to lose weight, perspire profusely, and have bouts of intermittent fever. This was associated with purulent sputum and hemoptysis. Chest X-ray at this time showed an area of increased density in the right upper lobe. His cortisone was stopped, and he was placed on streptomycin, with a provisional diagnosis of tuberculosis. However, his dyspnea continued to get worse. During the week previous to admission he became very short of breath on the slightest exertion, and developed sharp anterior chest pain, radiating down both arms and elbows, and relieved by sitting up. He was admitted to hospital on October 24, 1961. The history of past health revealed that he had passed a rigid physical examination by the American Draft Board in 1958. Of possible significance in the family history was the fact that his mother and two maternal uncles suffered from asthma.

Physical examination revealed an acutely ill, pale young man who was obviously dyspneic and perspiring profusely. He weighed one hundred pounds, fifty pounds less than he had three months previously. There was no cyanosis, but the jugular venous pressure was increased. The peripheral pulse was small, and a definite gallop rhythm was heard over the left sternal border, but no murmurs or pericardial friction rub. Rales were heard in the chest both anteriorly and posteriorly up to the angle of the scapula. The liver edge was palpable and slightly tender, but there was no evidence of ascites or peripheral edema. The neurological examination was negative. The temperature was 103°, the pulse was 140 per minute, and the blood pressure was 90/70.

Initial urinalysis showed albumin, 30 mg.%, with some red and white blood cells, and occasional casts. Initial blood work gave a haemoglobin of 83%, and a WBC of 13,000. The differential showed 60% neutrophils, and 16% eosinophils. The serum sodium and chloride estimations were at the low limits of normal. The C-reactive protein was positive. Total protein was normal, but serum albumin was low and beta and gamma globulins were slightly increased. The ECG showed low voltage sinus rhythm and diffuse T-wave changes. The chest X-ray showed gross cardiac enlargement and evidence of gross pulmonary edema. Thyroid function tests were normal. A pericardial tap yielded 10 cc. of clear fluid; nothing was found on microscopic examination and culture. He was placed on PAS and INH, with a provisional diagnosis of tuberculosis and idiopathic myocarditis.

His course in hospital was stormy. Soon after admission he developed abdominal cramps associated with loose stools, lasting ten days. On November 15 a dif-

fuse petechial rash appeared over the trunk and legs. His apical rate continued at 140 per minute with a gallop rhythm. The ECG remained unchanged. He was placed on Prednisone, 40 mg. daily. The temperature came down to normal.

A skin muscle biopsy on December 15 revealed only muscle atrophy. His weight loss continued. His tachycardia dropped to 100 per minute, while his blood pressure rose to 150/95. Serial chest X-rays showed a reduction in heart size and clearing of the lungs, although a reticular type of parenchymal change persisted in the right upper lung fields. Later X-rays showed the heart size reduced to normal, and almost complete clearing of the lungs.

He was discharged on December 21.

Final Admission — February 7, 1962

The patient was re-admitted because of wheezing, nausea, vomiting, and paresthesiae and a burning sensation in both legs. Examination revealed a very dejected and depressed man who was extremely cachetic. The heart rate was rapid but regular, and no gallop rhythm was heard, although a pericardial friction rub was noted. There were rales and rhonchi throughout the chest bilaterally, although it was felt that the bases were clear. The liver was palpable two finger breadths below the right costal margin, but non-tender. There was slight edema of the ankles. The pulse rate was 150 per minute, and the blood pressure was 110/70.

The urine showed albumin, 40 mg.% with 8-10 white cells per high power field, and a few coarse granular casts. The haemoglobin was 12.3%, the haematocrit 64%, and the platelet count 120,000/mm^3. The BUN was 25 mg.%, and serum electrolytes as follows: sodium—132 mEq/L, potassium—2.6 mEq/L, chloride—82 mEq/L, CO_2 C.P.—31.2 mEq/L. A chest X-ray showed parenchymal changes at the bases, with evidence of fluid in the pleural cavities. The heart was slightly enlarged. The ECG showed normal sinus rhythm at 160 per minute, but with a definite right axis deviation.

The patient did very poorly in hospital, and went rapidly downhill. The heart rate gradually increased to over 200 per minute, and the patient died on February 8, 1962.

II CLINICAL DISCUSSION

Here we have a man who suddenly developed a progressively severe pulmonary disease with involvement subsequently of most of the tissues of the body in some form of disease. He experienced remissions, but relapses were always more severe until the patient died less than two years after the initial onset. It is evident that we are dealing with a disease which is characterized by remissions, and which has the potential to involve many tissues in the body. Let us consider the course of this patient.

The first symptom noted in 1960 was the development of an intractable, non-productive cough which persisted even after he stopped smoking. Such a cough, presenting without any other symptoms, is suggestive of an allergy. This became somewhat worse in August, and the wheezing and lacrimation would suggest and support an allergic reaction, probably asthma. He was given steroids when the condition would not respond to bronchodilators. The use of steroids might seem a little premature, but the condition was probably severe, and steroids are often used to control severe asthma. His symptoms cleared, but the same picture returned a month later, with the addition of exertional dyspnea. His failure to respond to desensitization injections probably indicates a widespread allergy, since these injections are generally successful, at least for a time. Once again steroids were the resource, but the picture is complicated by the fact that the patient used them according to his own discretion and did not return to see his doctor as requested—a rather dangerous thing to do with steroids. There is a real danger of subtle overdose, as well as the reactions which may occur on regular doses, such as peptic ulcer, hyperglycemia, adrenal failure with stress, Cushing's syndrome, and a predisposition to infections. The history bears this out. The patient next presented (to another doctor) with severe symptoms of cough, dyspnea, weight loss, intermittent fever and heavy perspiration, associated with a purulent, bloody sputum. The symptoms suggest another allergic attack, but this time with an associated infection. X-rays showed an area of consolidation, suggestive of lobar pneumonia. Evidently tuberculosis was suspected, for the patient was put on streptomycin, although there is little evidence for tuberculosis. However, the treatment was effective.

The development of his chest pain is an important point in the history. Thus far the symptoms have been entirely pulmonary, but this pain which is relieved by sitting up is very suggestive of pericarditis. Coupled with this is an extreme weight loss—fifty pounds over three months. The picture of the patient on admission suggests a widespread disease process. The jugular venous pressure elevation and gallop rhythm would indicate heart failure. The presence of a small peripheral pulse suggests that the failure may be due to cardiac tamponade—the patient had symptoms of pericarditis. The tachycardia present may be due to simple compensation, but a myocarditis may also be present. The palpable liver is consistent with failure, although there was no ascites or edema. The tenderness would indicate recent failure. The X-rays and ECG are in keeping with a diffuse myocarditis causing a relatively quick development of cardiac enlargement. The urine suggests renal involvement, but as yet of a mild nature. The presence of higher titres of γ-globulin, and elevated

eosinophil count are indicative of a probable allergic process. At this point, we see that the patient has rales in his lungs, possible pericarditis, evidence of cardiac failure and myocarditis, renal involvement, with weight loss and a high WBC. The attention is directed to tuberculosis, but the renal lesions are against this. The WBC would suggest infection, but the problem is to find it. The question to be answered is, Can all these symptoms and signs be caused by a single disease entity affecting various organs, or are there several processes going on?

The fever continued, and two more significant symptoms developed—abdominal cramps, and loose stools, indications of gastro-intestinal lesions. Also a petechial rash was noted at this time. The chest lesions are confusing, with a constant flux, when seen on serial X-rays. The development of hypertension is significant, and is possibly due to renal ischemia, since it is of relatively sudden onset.

Again the patient experienced an almost complete remission, and was discharged. Although initially this seemed to be bronchial asthma with a pulmonary component such as Tuberculosis or possibly Loeffler's syndrome, all of the later symptoms and signs are consistent with the picture of polyarteritis nodosa, especially the renal, pulmonary, and cardiac lesions. The appearance of the rash, in the absence of a precipitating cause for it, should alert one to think of polyarteritis nodosa as a possible diagnosis.

The final admission was acute and of short duration. In addition to the reappearance of most of the former cardiac and pulmonary symptoms, burning and paresthesia appeared in both lower extremities. This is characteristic of a peripheral neuritis, although the evidence is not conclusive. The kidneys were also more severely affected. The patient died with severe tachycardia and rales bilaterally throughout the chest.

III PATHOLOGICAL DISCUSSION

Examination of the organs at autopsy revealed very little of significance on gross observation, considering the multiple symptoms of the patient.

The heart was the most significant, and weighed 395 grams, with a slight hypertrophy of the right ventricle, and dilation of the left ventricle. The myocardium appeared tough and brown, with small recent hemorrhages scattered diffusely throughout, appearing as small infarcts. The endocardium was scarred and there was a recent mural thrombus in the left ventricle. The pericaridum was smooth and glistening. The valves and coronary arteries were unremarkable.

The left pleural cavity contained 1000 cc., and the right pleural cavity 800 cc., of clear fluid. The left lung showed an old infarct in the lower lobe, while the right lung revealed a hemorrhagic meaty-looking consolidation on section, involving upper and lower lobes.

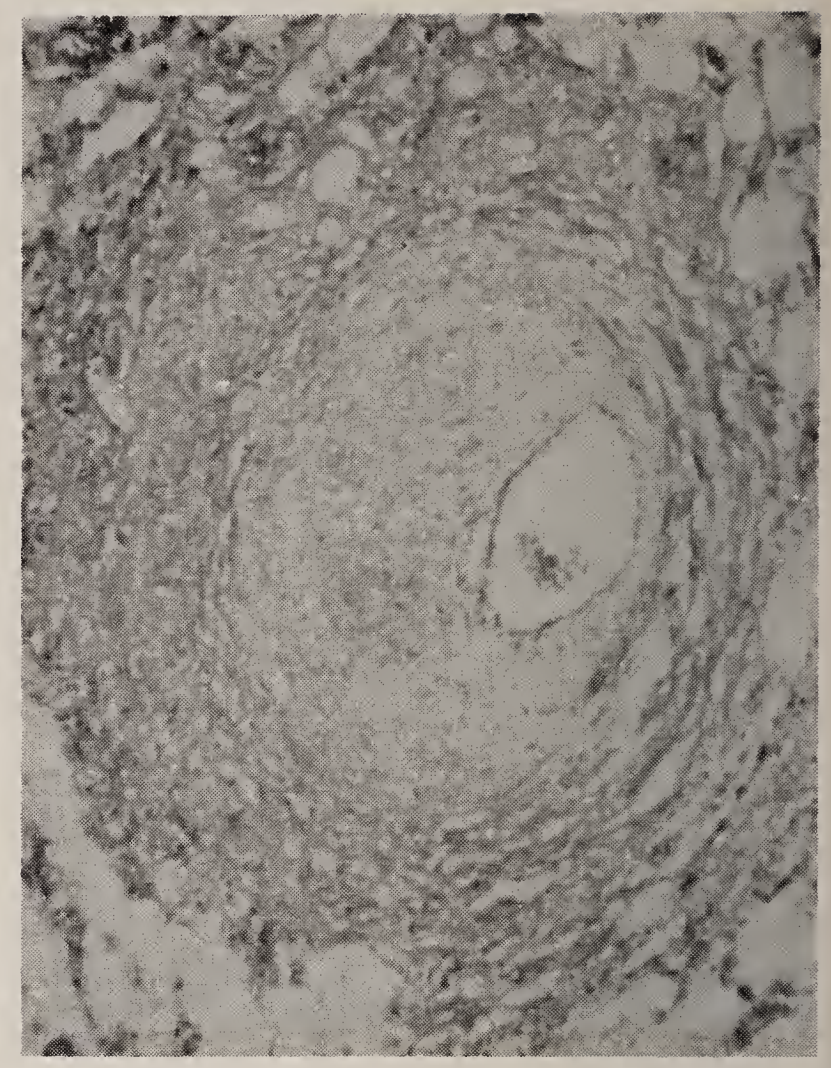

FIG. 1. A cross section of a medium sized artery exhibits an essentially healed arteritis characterized by collagen deposition in all layers and marked narrowing of the lumen.

The liver and spleen showed evidence of passive congestion, but the rest of the gross examination was unremarkable.

The microscopic examination gives us the diagnosis, and the cause of his multiple symptoms. When the organs were examined, they showed generalized polyarteritis nodosa of the arteries of the heart, kidneys, skin, and striated muscles. The heart, in addition, shows evidence of widespread severe myocarditis, attributable to polyarteritis nodosa. The vessels involved in the various organs showed varying degrees of endothelial proliferation, with adventitial, medial, and intimal fibrosis, and occasionally obliteration of the lumen. The lesions were mostly healed or in process of healing. Death was probably caused by the destruction of the myocardium, as revealed by the microscopic slides accompanying this article.

IV POLYARTERITIS NODOSA — DISCUSSION

Polyarteritis nodosa is a primary arteritis of obscure etiology characterized pathologically by inflammation and fibrinoid necrosis of medium-sized and small arteries and clinically by a variable multi-system disorder, the manifestations of which depend on the location of

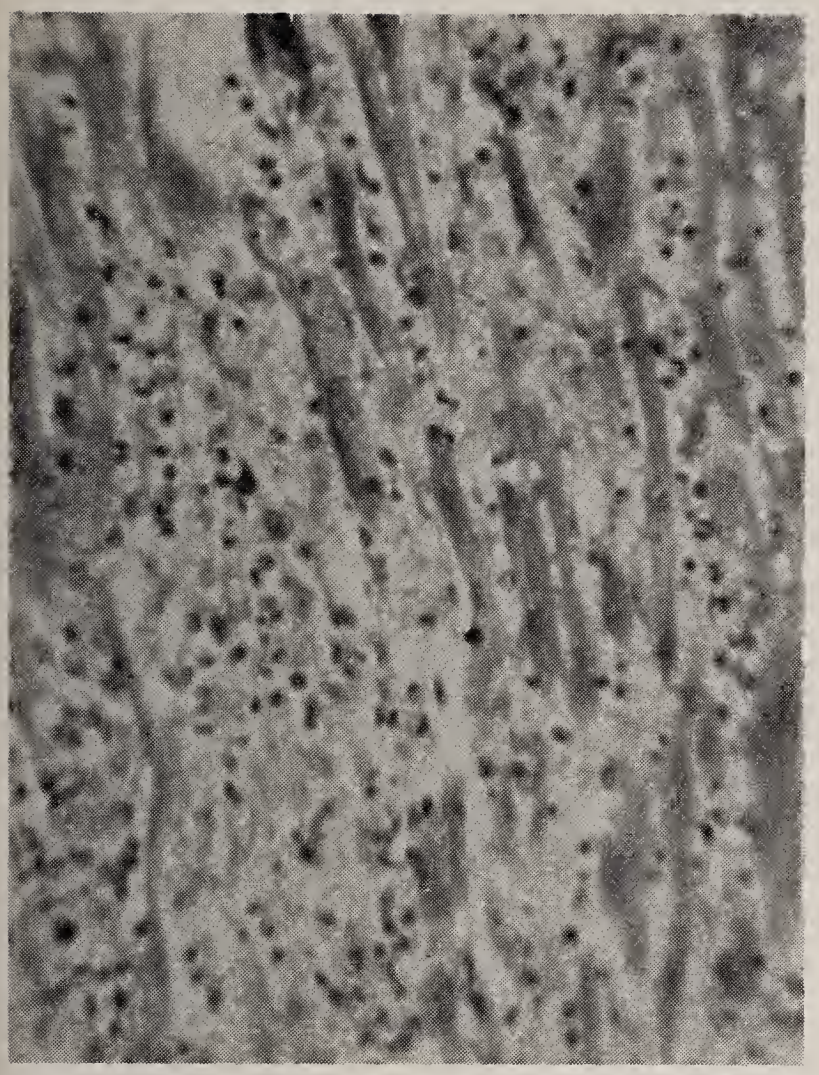

FIG. 2. This section of myocardium exhibits an area where recent necrosis is present, accompanied by an influx of acute inflammatory cells. These areas are considered secondary to arteritis and occlusion of small regional arteries.

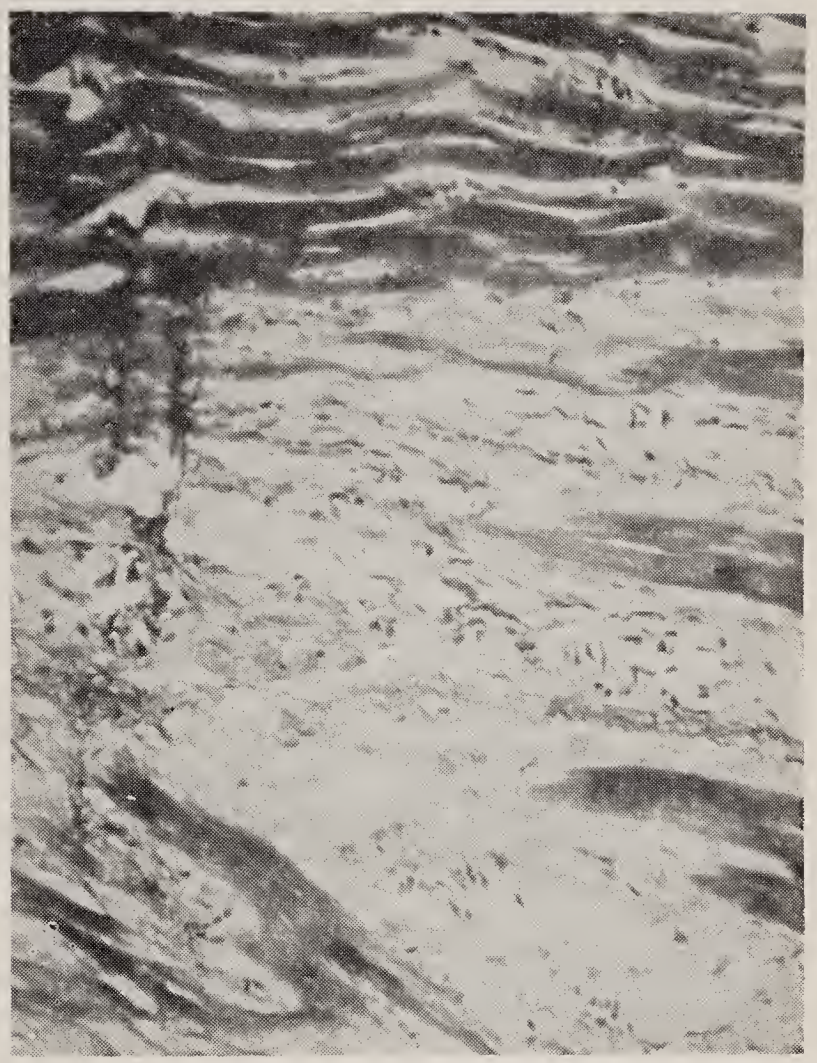

FIG. 3. As seen in this slide, the bulk of the cardiac pathology consisted of areas of myocardial fibrosis, replacing areas of previous focal necrosis, as shown in Fig. 2.

the histological lesion. It is a relatively uncommon disease occuring most frequently in the 20-50 yr. age group, and contrary to the other collagen disorders in which females predominate, three times more frequently in males.

Pathologically the medium-sized and small arteries, and occasionally veins and capillaries, show necrosis, fibrinoid change and leukocyte infiltration. This process is segmental, begins in the media and extends to the intima disrupting the internal elastic lamina. Initially, there is polymorphonuclear leukocyte infiltration with some degree of eosinophilia; later there is mononuclear cell infiltration and finallly fibrosis. The vessels demonstrate various stages: coagulation necrosis with acute inflammation, healing, excessive fibrosis forming nodules, intimal proliferation resulting in thrombosis, weakening and aneurysmal dilatation of the arterial wall, or arterial dissection. These may be seen in any organ, most commonly the kidney and heart, but also the lungs, liver, spleen, gastro-intestinal tract, adrenals, testes, brain and peripheral nerves. This disease is thought to be due to some disorder in the immune mechanism and may be a general response to hypersensitivity. Similar lesions with demonstrable γ-globulin are seen in allergic reactions described as hypersensitivity angiitis. It may be related to a reaction to some drug or an abnormal response to a bacterial or viral agent.

The clinical picture is variable which may begin abruptly or show a gradual onset often after a previous illness. It is a progressive disorder which may show remissions and exacerbations. Clinically any of the following may occur:

—generalized symptoms of fever, weight loss, anorexia, headache and fatigability.

—a primary disease of kidney similar to glomerulonephritis with backache, nocturia, hematuria and proteinuria.

—unexplained hypertension.

—abdominal manifestations which may simulate an acute abdomen with severe periumbilical or right upper quadrant pain, anorexia, nausea, vomiting or diarrhea.

—bronchial asthma or focal pulmonary infiltration suggesting infection.

—myocardial infarction, coronary insufficiency, myocarditis or episodes of pericarditis.

—muscle aching, tenderness, weakness and wasting.

—skin or subcutaneous nodules, urticaria, purpura or other skin rashes.

—involvement of peripheral nerves; CNS disturbances with behavioral disturbances, headache, convulsions, subarachnoid hemorrhage, or motor or cerebellar disturbance.

—involvement of the eyes with direct involvement of the vessels with hemorrhage and exudates or secondary changes of hypertension.

—arthralgia or rarely arthritis.

—hepatomegaly with some cases of jaundice.

The laboratory is not very helpful in making a precise diagnosis. There is often an anemia due to blood loss, secondary to renal involvement, or hemolytic in character. There is usually a polymorphonuclear leukocytosis with some degree of eosinophilia. Urinalysis will show proteinuria with red cells, white cells or casts. The erythrocyte sedimentation rate (ESR) is usually elevated with raised serum globulins and lowered albumin levels. A chest X-ray may show areas of consolidation, miliary opacities or cavitation, cardiomegaly or rarely pleural effusions. The ECG may show evidence of heart disease. The diagnosis can only be made from skin-muscle biopsy which should be performed in the involved areas and which may be positive in only one third of cases.

PAN is characterized by remissions and exacerbations, but is a progressive disorder with death often resulting within weeks or months of diagnosis. 10% may live longer than one year with some living 7-10 years. The cause of death may be due to renal failure with uremia, hypertension, or coronary or gastro-intestinal artery disease. The disease is treated symptomatically with analgesics, blood transfusions, digitalis, sodium restriction or anti-hypertensives. Large doses of steroids may control the clinical and pathological picture and may produce some long term remissions but basically only prolong the inevitable end.

The presented case of a young man with a rapidly progressive disease showing the general symptoms of profound weight loss and involvement of many systems may be considered as a "fairly typical" case of polyarteritis nodosa.

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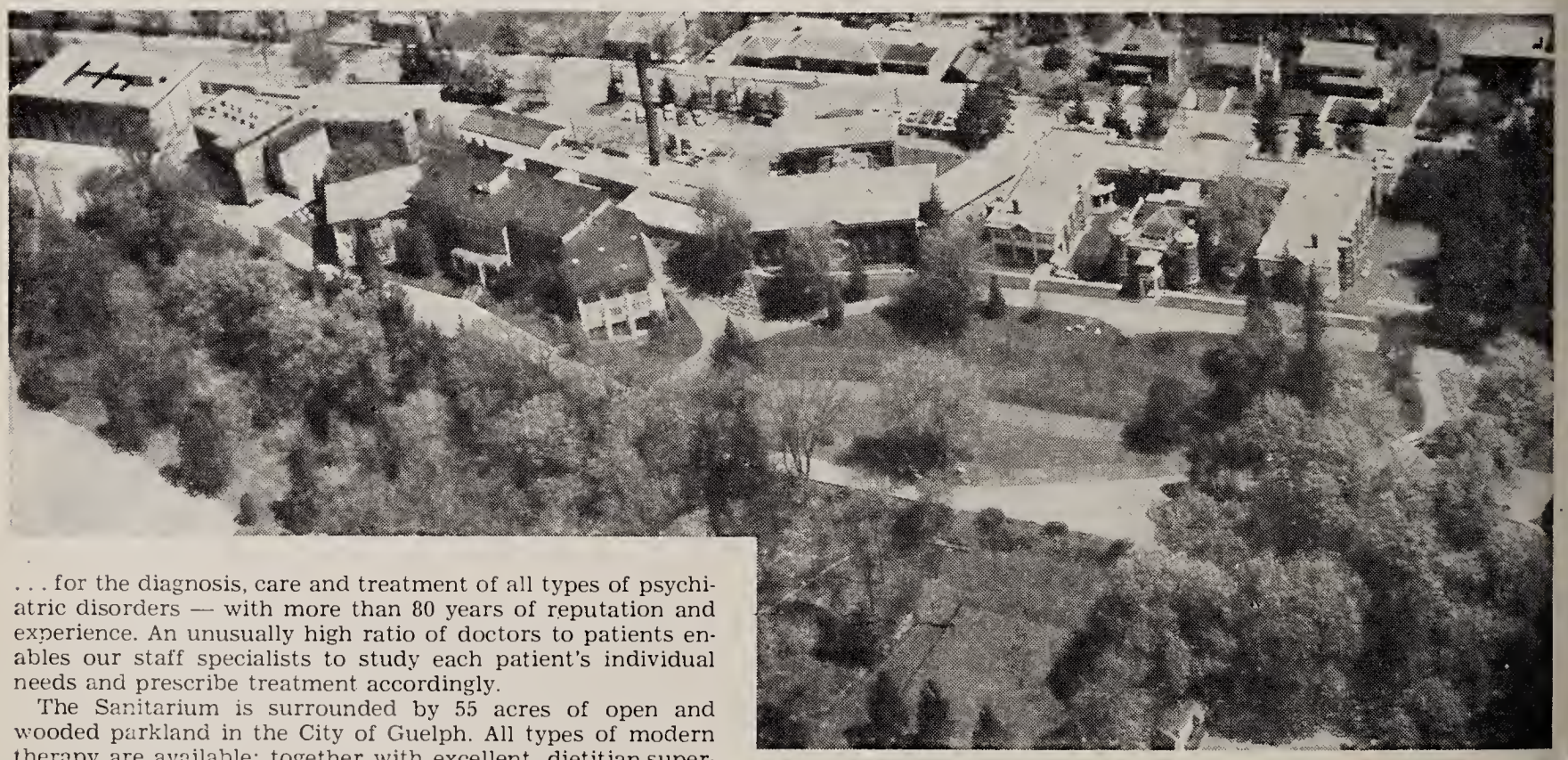

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Book Reviews

OF MOLECULES AND MEN

Francis Crick. 99 pp. University of Washington Press, Seattle and London. 1966. $3.95.

Dr. Crick needs no introduction in this or any other scientific publication, for the effect of his work and that of his associates have been felt in nearly every scientific discipline. In this book he presents, in relatively lay language, a review of his achievements, and assaults the "ivory tower" of philosophy. In the latter endeavour, he is primarily concerned with refuting the doctrine of Vitalism, which holds that there exists some force, incomprehensible in terms of physics and chemistry, which influences the direction and development of biological systems. In Crick's view this "force" is nothing more than an attempt by some philosophers and scientists, to deny our ignorance regarding certain biological phenomena.

He points out that the major areas of ignorance, hence the remaining strongholds of Vitalism, are threefold: the distinction of "living" from "non-living", the origin of life, and consciousness. Also, in the past there have been at least two other areas of conflict between science and Vitalism, since resolved; namely, the distinction between "organic chemistry" and "inorganic chemistry", and the explanation of the energy produced by living things.

The first two problem areas obviously pertain to his work with D.N.A. and here the influence of Vitalism is virtually extinct. The scientific investigations of consciousness, on the other hand, is still relatively primitive; the inevitable comparison of electronic computers and the human brain is brought up although the grounds for comparison are surprisingly few.

The book is based on the fifth series of John Danz lectures, given at the University of Washington. It is significant that a man of Crick's scientific stature does not allow a dichotomy of science and philosophy, and, for students of both, this book provides interesting reading.

R.L.W.

THE CONTROL OF INFECTION IN HOSPITALS

W. Harding Le Riche, Carolee E. Balcom, Gerald van Belle. xii + 341 pp. University of Toronto Press, Toronto. 1966. $9.00.

This book is a report of the investigation conducted by Prof. Le Riche and Miss Balcom of the School of Hygiene, and Mr. van Belle of the Dept. of Mathematics, into the procedures of infection control in hospitals, mainly in Ontario. This consisted of a questionnaire survey of 208 Ontario hospitals, and intensive study, through personal observation by Miss Balcom, of aseptic practice in six of these hospitals. Mr. van Belle carried out a statistical analysis of the data obtained, and 164 of the hospitals were evaluated on the basis of their replies. The hospitals remained anonymous throughout the study.

The problem of cross-infection, that is, infection arising subsequent to admission, is attacked from a variety of aspects—hospital design, housekeeping, nursing and surgical practice, laundry, etc., and throughout the book, recommendations and suggestions are made to improve existing conditions. Also the authors have not hesitated to offer examples poor and sometimes shocking conditions.

On first reading, one gets the impression that the expense and time involved in eliminating all sources of contamination render this aim impractical and unattainable, but the point is this: cross-infection does occur and is an important factor in patient mortality as well as patient turnover, hence efforts must be made to reduce its incidence, for it, too, is expensive and time consuming. The authors have pointed out the sources and possible corrective measures, maintaining that the realization of asepsis is not impossible, but merely difficult.

R.L.W.

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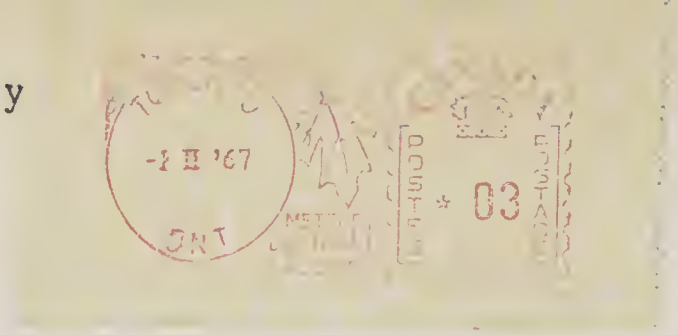

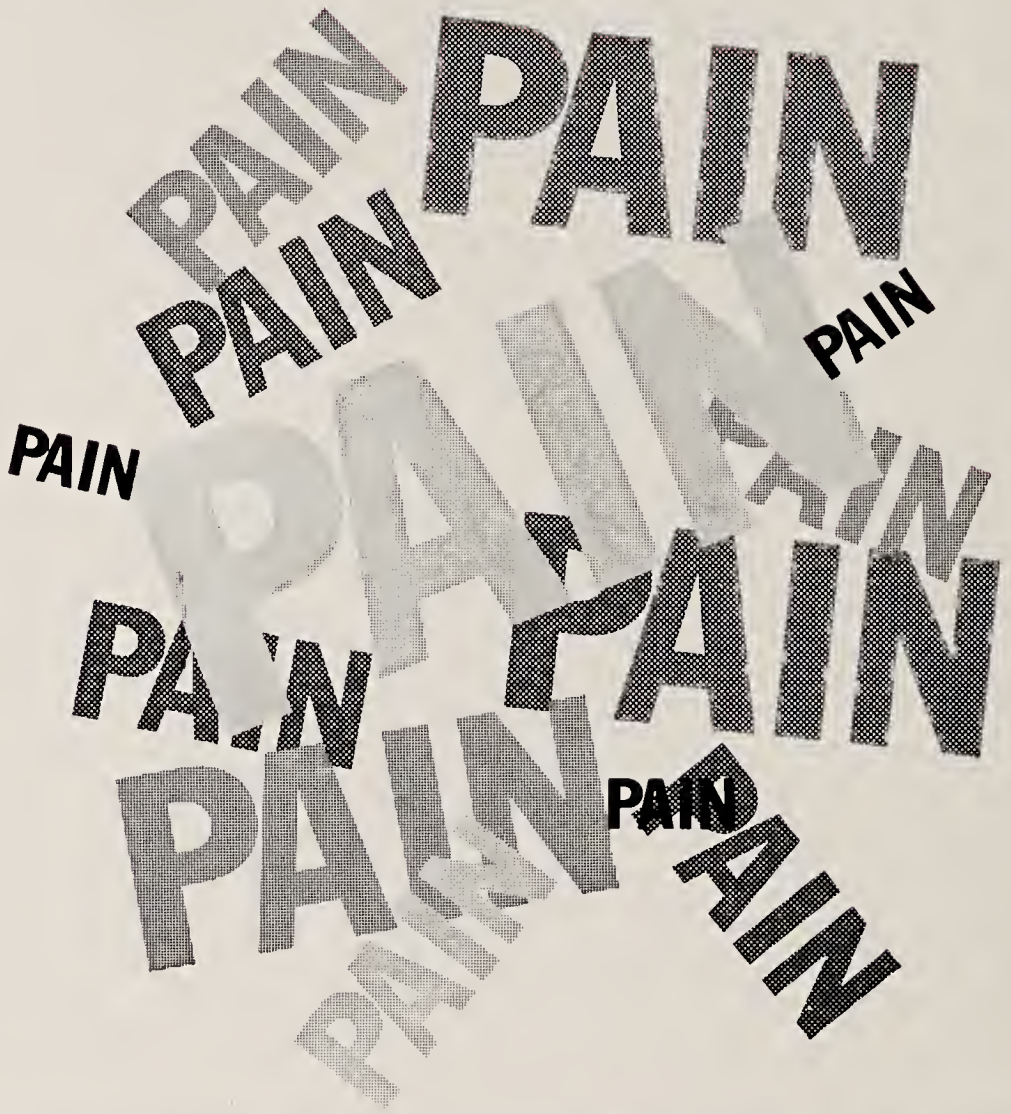

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